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PERMANENT ADDRESS:

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...

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SYNTHESIS AND REACTIONS OF CHIRAL SULFONIUM YLIDS

by

© STEWART JOHN CAMPBELL

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled 'Synthesis and Reactions of Chiral Sulfonium Ylids' submitted by Stewart John Campbell, B. Sc., in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Organic Chemistry.

Karl B. Kopecky
Supervisor

External Examiner

Date Fall 1973

ABSTRACT

The principles of optical isomerism were applied to a study of the stereochemical aspects of a novel class of organosulfur compounds, the chiral sulfonium ylid. The first synthesis of such an ylid was reported in 1968 by Darwish and Tomilson (9) when (-)-ethylmethylsulfonium phenacylid ((-)-5) was prepared from (-)-ethylmethylphenacylsulfonium perchlorate ((-)-15).

Several reactions of (-)-5 which retained the chiral sulfonium center in the product were devised. These included: treatment with acetic anhydride to give (-)-ethylmethylsulfonium acetylbenzoylmethylid ((-)-10); treatment with benzoic anhydride and phenyl isocyanate to give the corresponding methylids (-)-9 and (-)-11; and O-alkylation with dimethyl sulfate to give (+)-ethylmethyl-α-methoxy-β-styrylsulfonium methyl sulfate ((+)-13). Resolution of the corresponding (+)-13 using dibenzoyltartaric acid monohydrate as resolving agent gave the corresponding (+) and(-)-vinyl perchlorates plus the unexpected products from the Michael-addition of methanol solvent to the vinyl-sulfonium salt, (-) and (+)-ethylmethyl-2,2-dimethoxy-2-phenylethylsulfonium perchlorate. The rates of racemization of these sulfonium ylids and salts were studied. The results of these kinetic studies are discussed in the light of current pyramidal inversion theories.

The ability of chiral sulfonium ylids to effect an asymmetric transfer was tested by treatment of optically active ethylmethylsulfonium p-nitrobenzylid ((+) and (-)-22) derived from (+) and (-)-ethylmethyl-p-nitrobenzylsulfonium perchlorate ((+) and (-)-21) with aldehydes and ketones. The ylid (-)-22 was found to undergo a nucleophilic reaction with benzaldehyde to provide trans-p-nitro-

stilbene oxide, however, the extent of asymmetric transfer was negligible as nearly racemic oxirane was obtained. The ylid (+)-22, in failing to react with ketones, underwent the Sommelet rearrangement to (+)-methyl α-(2-methyl-5-nitrophenyl)ethyl sulfide ((+)-34) and ethyl 2-methyl-5-nitrobenzyl sulfide (33). The Sommelet rearrangement of (R)-(+)-ethylmethyl-p-chlorobenzylsulfonium perchlorate provided the analogous chlorosulfides (+)-41 and 42.

The efficiency of the asymmetric transfer in these Sommelet rearrangements was assessed by determining the enantiomeric and optical purities of (+)-34 and (+)-41. The enantiomeric purities of these sulfides, determined as their corresponding sulfones using the chiral shift reagent $Eu(hfbc)_3$, were found to be 19.5 ± 0.7 and 27.5 ± 1.2% respectively. These values of enantiomeric purity compared favourably with values of optical purity obtained by comparison of the specific rotations of the rearrangement derived sulfides with the absolute rotation of resolved samples obtained by independent methods.

Examination of the reactive conformations of the benzylids from (R)-(+)-35 expected to lead to product and of the projections of the cyclic transition states from these conformations has permitted the sulfide (+)-41 to be assigned the S absolute configuration.

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CHAPTER ONE

INTRODUCTION

Studies in optical isomerism have contributed immensely to the understanding of organic stereochemistry. In order to probe reaction mechanisms, to devise chemical synthesis and to formulate conformational relationships, scientists have applied the classical principles of optical isomerism. This thesis will describe a study of some of the stereochemical aspects of a novel class of organosulfur compounds, the chiral sulfonium ylid.

Before proceeding to the text, however, a short introduction to the history and principles of optical isomerism as applied to this research and of nomenclature of the sulfur compounds of interest is desirable. Several authors have recently published excellent texts and articles worthy of mention dealing with subjects related to optical isomerism:

E. L. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill, New York, 1962.

K. Mislow, Introduction to Stereochemistry, Benjamin, New York, 1965.

K. Mislow and M. Raban, Stereoisomeric Relationships of Groups in Molecules, in Topics of Stereochemistry, Vol. 1, pp. 1 - 38, ed. E. L. Eliel and N. L. Allinger, Interscience Pub. Inc., New York, 1967.

J. D. Morrison and H. S. Mosher, Asymmetric Organic Reactions, Prentice-Hall, Inc., New Jersey, 1971.

E. L. Eliel, Recent Advances in Stereochemical Nomenclature, J. Chem. Ed., 48, 163 (1971).

S. H. Wilen, Resolving Agents and Resolution in Organic Chemistry, in Topics of Stereochemistry, Vol. 6, pp. 107 - 176, ed. E. L. Eliel and N. L. Allinger, Interscience Pub. Inc., New York, 1972.

The historical events, definitions and examples mentioned in this introduction can be found in these references and are cited without specific referral either to the review or to the original publication.

In 1815, J. B. Biot was the first to observe that solutions of some naturally occurring organic compounds rotated the plane of polarized light. The first resolution of a racemic modification into its optical enantiomers was accomplished by Louis Pasteur in 1848 by the mechanical separation of the two kinds of crystals of sodium ammonium tartrate formed during the slow evaporation of an aqueous solution of the salt at room temperature. As was later shown, had the ambient temperature during the evaporation been above 27°, a racemic compound would have precipitated rather than the gross mixture of crystals of each enantiomer. This earliest example of a resolution illustrates the subtle experimental conditions that a chemist sometimes encounters in establishing the necessary conditions to resolve a compound. As there are no assured methods of performing a particular resolution, an extensive series of pilot projects involving a trial and error approach using established techniques is usually required.

The favoured approach to resolving a racemic modification involves the formation and separation of a diastereomeric mixture from an optically active resolving agent and the racemic compound. If, for

example, the racemate (±)-A is treated with (+)-B, the diastereomeric mixture of (+)-A(+)-B and (-)-A(+)-B is formed. As diastereoisomers are different compounds, their slightly different physical properties often facilitate their separation. The resolution is completed with the regeneration of the (+) and (-) enantiomers from their pure diastereoisomers. Diastereoisomers have most frequently been separated by the fractional crystallization of the less soluble isomer. Occasionally such an efficient separation occurs that the more soluble isomer can be readily obtained pure from the mother liquor of the original crystallization. Chromatographic separation of diastereoisomers is being used in more specialized instances today, particularly with the improved instrumental technology available.

The resolving agents most frequently employed are naturally occurring compounds or derivatives thereof. Many synthetic resolving agents in pure forms are now available to the modern chemist. The synthetic agents are often available in both isomeric forms thereby facilitating the resolution of both isomers of a racemate when recovery of the more soluble diastereoisomer during a fractional crystallization is inefficient. This principle of using enantiomeric resolving agents was recognized by Markwald in 1896. Diastereomer formation can involve the production of a salt, of a covalently bonded derivative such as an ester, or of complexes. The ester method has the disadvantage in that crystalline derivatives are less frequently encountered than for the salt method. Chromatographic resolutions can, however, be performed on the covalently bonded diastereoisomers.

Partial resolutions of racemates have been achieved by the selective removal of one enantiomer during a reaction involving

diastereomeric transition states and by the faster cleavage of a particular diastereoisomer of a diastereomeric mixture to enrich the product with one enantiomer at the expense of the other. Of current interest today is the use of enzymes to effect these types of kinetic resolutions.

The optical purity of a partially resolved compound can sometimes be increased by separating the racemate from the active isomer by repeated fractional crystallizations. Optical purity is defined as the specific rotation, $[\alpha]$, of a substance divided by the absolute rotation, $[A]$, the specific rotation of the pure enantiomer, eq. [1].

$$\% \text{ optical purity} = \frac{[\alpha]}{[A]} \times 100 \qquad [1]$$

Enantiomeric purity refers to the excess of an enantiomer over its corresponding racemate as a percentage of the mixture as a whole. Hence values of enantiomeric purity and optical purity are the same for a compound as optical purity is simply an experimental measurement of the excess enantiomer. Two basic criteria for regarding a resolution complete are the constancy of melting points and of optical rotations upon consecutive recrystallizations of the enantiomer and precursor diastereoisomer and equal and opposite absolute rotations for the two enantiomers, if available. In applying these criteria the chemical purity of the samples must be assured as impurities that may not have been removed from the sample during the resolution can bias the optical rotation measurements.

Spectroscopic methods of determining enantiomeric purity which

are fast and reliable are increasingly important today. The progress of a resolution can be monitored by observing the disappearence of one set of absorptions in the N.M.R. spectra due to diastereotopic atoms of a mixture. Enantiomeric purity can be determined by quantitatively converting an enantiomeric mixture to a diastereomeric mixture by use of a chiral reagent and recording the N.M.R. spectrum of the product. Assuming care is taken to prevent enantiomeric or diastereomeric enrichment during this procedure, the relative integrations of the diastereotopic protons indicate the enantiomeric purity of the original mixture. The diastereoisomers formed can be covalently bonded molecules or transient complexes distinguishable on the N.M.R. time scale. The N.M.R. method of analysis in many instances eliminates the sometimes tedious and expensive procedure of determining optical purity by the classical method of comparison with authentic samples that often must be synthesized.

The successful resolution of a chiral molecule requires that the enantiomer be optically (enantiomerically) stable at normal operating conditions. No racemization should occur during the regeneration of the enantiomers from the resolved diastereoisomers. Racemization is a process of interconverting one enantiomer to its partner whereby, in time, a racemic modification is produced. Racemization occurs upon the reversible production of a symmetrical intermediate such that the stereochemical integrity of the center of chirality is lost. A racemization process is often followed by observing the loss of optical activity of solutions of the chiral substrate. However, the rate of loss of optical activity cannot be equated with the rate of racemization if the chiral substrate undergoes decomposition to products other than

its enantiomer.

The origin of optically active compounds is a fascinating subject that has likely been discussed since the earliest observation of optical activity. Optical activity is now recognized to be such an inherent feature of life that the failure of other planets to yield active material may be taken as evidence for the absence of life of complexity comparable with the earth's (1). There have been a few examples of the spontaneous resolution of racemates into their optical isomers; however, in all but a recent case, the inabliity to obtain experimentally nearly equal distributions of enantiomorphs suggested there to be some undefined dissymmetric influence affecting the crystallization process. R. E. Pincock, et al have recently described the spontaneous generation of optically active (+) and (-)-1,1'-binaphthyl upon crystallization of the active isomers from the racemate's melt (2). Thus, in two hundred crystallizations, the sum of the observed specific rotations was $[\alpha]_{589}$ $+0.14^{\circ}$, while the maximum observed rotations were $[\alpha]_{589}$ $+206^{\circ}$ and -208°. In practical terms, it remains that an asymmetric environment is required to effect an asymmetric synthesis, as a synthesis of chiral molecules in the total absence of an asymmetric physical environment is expected to produce a racemic modification. Mosher defines an asymmetric synthesis as a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reaction into a chiral unit in such a manner that stereoisomeric products are produced in unequal amounts. This definition is in principle the same as that originally proposed by Marckwald in 1904.

Although nature is well known to synthesize many enantiomers to the exclusion of their isomers, the chemist only occasionally accomplishes this in a laboratory synthesis. Per cent asymmetric synthesis is defined as the extent to which one enantiomer is produced in excess over the other and is numerically equal to optical purity or diastereomeric purity. The ability of a chiral center to induce a particular geometry at a nearby developing center of chirality in an asymmetric synthesis has been related to the stereochemical and electronic effects of the inducing chiral center on the environment at the new center. In a self-immolative reaction, in which an inducing center is destroyed at the same time that a new chiral center is formed, the enantiomeric ratio of products is attributed to the energy differences of the diastereomeric transition states leading to each enantiomer as there are no free energy differences in either the products or the reactants, see Figure I. Therefore, the greater the free energy difference of the transition states, the higher the efficiency of the asymmetric transfer.

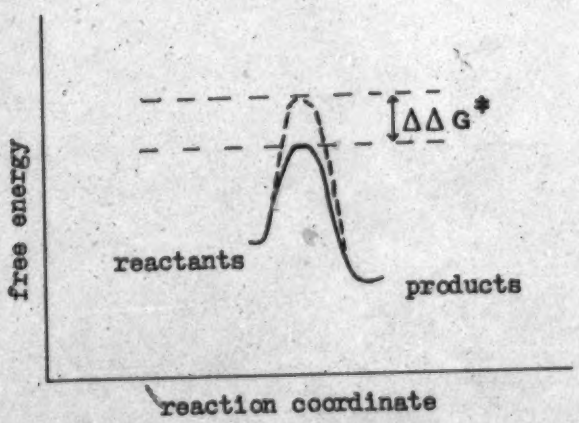
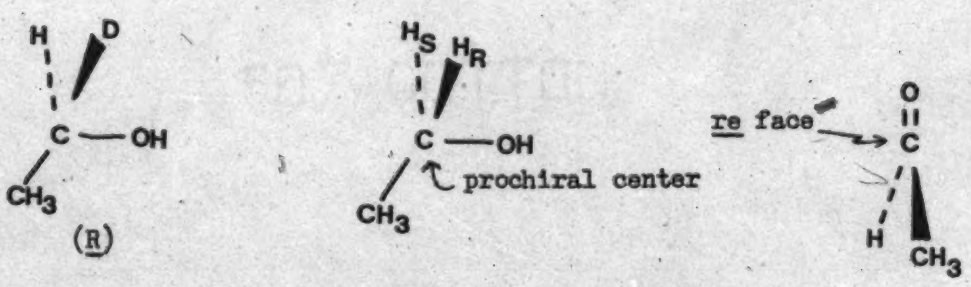


Figure 1. Energy profile for a self-immolative reaction.

Pasteur realized that the activity of a compound was caused by the asymmetric arrangement of atoms in the molecule. J. A. LeBel and J. A. van't Hoff in 1874 explained the optical activity of many organic compounds as a consequence of a tetrahedral, asymmetrically substituted carbon atom. Emil Fischer in 1890 developed the projection formula to represent asymmetrically substituted atoms. Not until 1951 was the sign of rotation of an enantiomer correlated with its absolute configuration when J. M. Bijvoet determined the structure of sodium rubidium tartrate by X-ray crystallography. Prior to then, the structural correlations had been arbitrarily assigned based on (+)-glyceraldehyde having the R configuration. Fortuitously, the assignment of absolute configuration had been correct. A correlative method of determining configuration involves the comparison of a compound with that of another whose configuration and sign of rotation are known. The comparison often requires a chemical degradation of one of the pair in a series of reactions not involving the asymmetric center or involving the center only in a predictable manner. Absolute configuration has also been assigned from reactions involving asymmetric synthesis and kinetic resolutions based on the known stereochemical effects of substitent groups on an asymmetrically substituted carbon atom.

The R-S configurational nomenclature referred to is that proposed by Cahn, Ingold and Prelog for the systematic recording of the absolute configuration of chiral molecules. This system has been extended by K. R. Hanson to designate paired stereoheterotopic ligands of a tetrahedrally substituted atom such as the hydrogen atoms of the methylene carbon of ethanol. These hydrogens are designated as pro-R (H_R) and pro-S (H_S) and the carbon center as a prochiral center. An assembly is

prochiral if a chiral assembly is obtained when a ligand in a non-chiral assembly is replaced by a new ligand. Thus a pro-R ligand is that which upon elevation in priority gives the R configuration. Hanson has also provided a system for designating the two faces of a trigonal atom such as that of acetaldehyde. If the priority sequence of the ligands starting with the ligand of highest priority is seen to be clockwise, then the re face of the trigonal atom is observed; if anticlockwise, then the si face is observed. These latter rules are not concerned with the chirality of the products of any reaction involving a trigonal atom, but only with the topology of the molecule containing such an atom. The nomenclature systems are illustrated below:

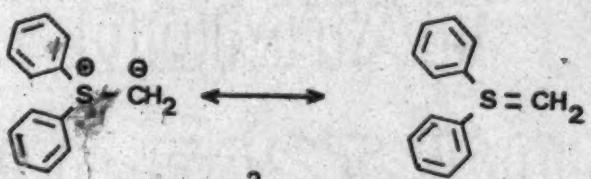


As indicated, these basic concepts of optical isomerism were applied to a study of the stereochemical properties of sulfonium ylids. A. W. Johnson in the introduction to his book Ylid Chemistry outlines the various nomenclature systems used by various authors in the literature (3). The word ylid is derived from the ending yl which implies an open valency, i. e. methyl, benzyl, benzoyl, etc., and the ending id implying anionic character, i. e. methide. Therefore a sulfonium ylid is defined as a compound containing a carbanion which is directly substituted with a positively charged sulfonium group, eq. [2].

[2]

1a 1b

The suffix ylene has been used in specific reference to the resonance structure 1b in which the sulfur valency has been expanded to 10 electrons thus implying partial double bond character. A third system is based on the hypothetical fully substituted neutral species SH_4, sulfurane. As an example of these nomenclature systems the compound 2 is named:



2

a: diphenylsulfonium methylid

b: diphenylsulfonium methylene

c: diphenylsulfuranylmethane or diphenylmethylenesulfurane

Although the last system is favoured by A. W. Johnson, the first nomenclature system has been adopted exclusively in this thesis: first, as it is the classical system; but more importantly, as it more readily denotes the asymmetry and nucleophilicity inherent in these types of compounds.

In Chapter Two, some reactions of a crystalline optically active sulfonium ylid will be discussed. Several new ylids were synthesized and a study of their optical stability performed. The third chapter will describe the use of reactive chiral sulfonium ylids as agents capable of asymmetric transfer. Finally, Chapter Four concludes experiments on asymmetric induction by determining the extent of asymmetric transfer in the Sommelet rearrangement of two benzyl sulfonium salts.

CHAPTER TWO

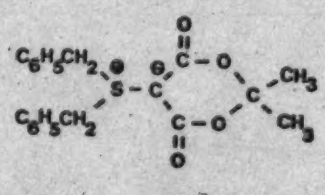
OPTICALLY ACTIVE SULFONIUM YLIDS

Introduction

The first sulfonium ylid, dimethylsulfonium fluorenylid was prepared by Ingold (4) in 1930 by the reaction of the conjugate acid bromide with base. A number of stable sulfonium ylids have been prepared since 1930, the chemical properties of which have been extensively studied (3).

Although the first resolution of a sulfonium salt was reported by Pope and Peachey (5) in 1900, failures in resolving sulfonium ylids were reported as late as 1966. Nozaki, et al (6), for example, obtained racemic methylphenylsulfonium p-iodophenacylid upon basic treatment of (-)-p-iodophenacylmethylphenylsulfonium picrate.

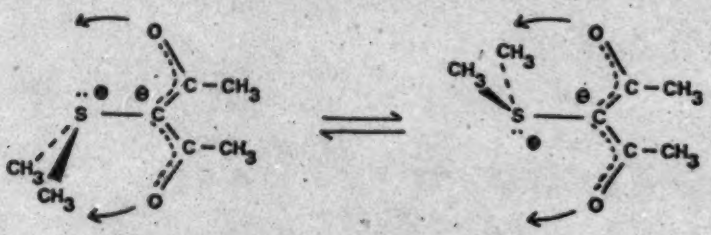
The pyramidal configuration of sulfonium ylids has been confirmed by N.M.R. spectroscopy (7) and X-ray crystallography studies (8). The N.M.R. spectra of 3 showed the methylene protons of the S-benzyl groups of be non-equivalent, hence diastereotopic, even at 100° (7b).



3

Nozaki, et al (7c) reported an N.M.R. spectral study of dimethylsulfonium diacetylmethylid 4. This compound exhibited magnetic equivalence of the two acetyl-methyl groups at room temperature. However they became differentiated at lower temperatures, the coalescence temperature being ca. -25°. This result was interpreted as evidence for a rapid exchange of 4a and 4b at room temperature, with the exchange being slowed down considerably at lower temperatures. The exchange

was suggested to occur through either internal rotation around the S—C bond or inversion at the sulfur pyramid with the authors favouring the latter. The average life time of each conformer was estimated to be ca. 0.02 seconds at -25°.



4a 4b

Recently, Darwish and Tomilson (9) reported the preparation and facile racemization via pyramidal inversion of (-)-ethylmethylsulfonium phenacylid (-)-5. The ylid (-)-5 was found to have a half-life of racemization of ca. 30 minutes at 50° in benzene. In view of this latter report, Nozaki's interpretation of the kinetic process studied in 4 appears to be incorrect. That is, it seems unlikely that pyramidal inversion in 4 could be occurring at such a rapid rate. However, one might be able to rationalize it on the following basis. The rates on pyramidal inversion reactions in sulfonium salts are known to be susceptible to steric acceleration (10,11). If a diacylmethylid (as in 4) was very much larger sterically than a phenacylid (as in 5), an analagous steric factor in sulfonium ylids might result in a much faster pyramidal inversion for 4 than for 5. Furthermore, the pyramid of 4 may have assumed a more planar arrangement because of stabilization due to the coulombic interactions between the electron-rich oxygen atoms of the diacylmethylid and the positive sulfur atom as indicated in 4a and 4b, thereby lowering the activation energy for pyramidal inversion. It was desirable therefore to prepare derivatives of (-)-5 which would test Nozaki's interpretation of the kinetic process involved.

Synthesis and Resolution

(-)-Ethylmethylsulfonium phenacylid ((-)-5) was prepared according to the procedure of Darwish and Tomilson (9). Figure II outlines the route which was followed for the resolution procedure.

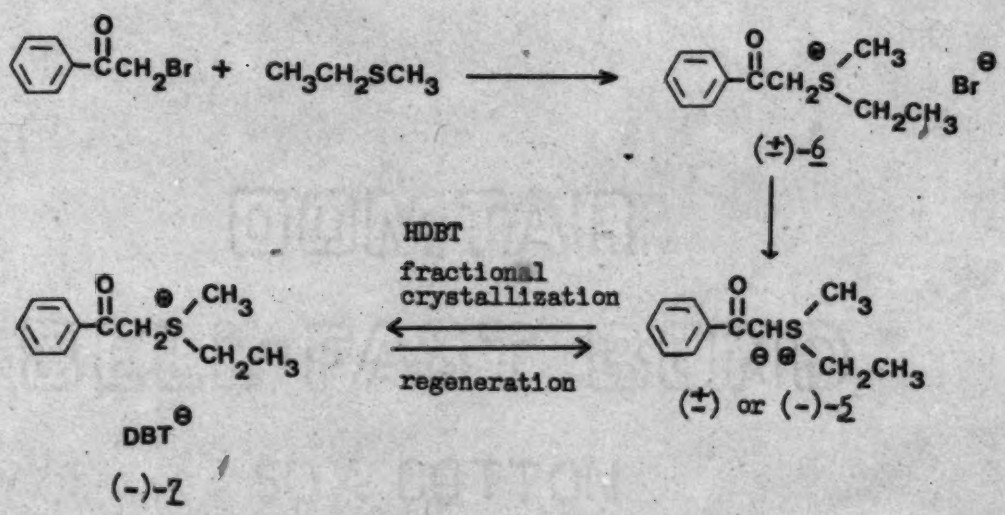


Figure II. Synthetic route to (-)-ethylmethylsulfonium phenacylid.

(±)-Ethylmethylphenacylsulfonium bromide (6) was prepared by the reaction of phenacyl bromide with ethyl methyl sulfide in acetone solution. The salt was precipitated as an oil upon the addition of ether. The racemic ylid was generated by basic treatment of the crude bromide salt and extraction of the basic solution with chloroform. The evaporation residue from the chloroform extracts was crystallized from a benzene-Skellysolve B solvent mixture to yield racemic ethylmethylsulfonium phenacylid ((±)-5).

The ylid was resolved by the diastereomeric salt method using (-)-2(R),3(R)-dibenzoyltartaric acid monohydrate (HDBT) (12) as the resolving agent. Repeated crystallization of the diastereomeric salt mixture from methanol at 5° gave the optically pure, less soluble (-)-ethylmethylphenacylsulfonium hydrogen 2(R),3(R)-dibenzoyltartrate ((-)-7), $[\alpha]_{589}^{RT}$ - 90.2° (c 0.56, methanol) (reported $[\alpha]_{589}^{RT}$ - 88.2° (c 0.44, methanol) (13)).

Treatment of the resolved DBT salt with dilute base, rapid workup and crystallization of the recovered oil yielded (-)-5, $[\alpha]_{589}^{RT}$ - 216° (c 0.419, benzene) (reported $[\alpha]_{589}^{25}$ - 137° (c 0.487, benzene) (9)). The observed rotation of the ylid was considerable higher than the previously reported value due to a more efficient resolution and isolation procedure. Other data supporting the structure of this compound compare with the reported data. Reactions of (-)-5 were conducted using material with specific rotations of ca. $[\alpha]_{589}^{RT}$ - 180°, as the final recrystallizations in the resolution were extremely tedious.

Reactions of (-)-Ethylmethylsulfonium Phenacylid

Sulfonium ylids react as nucleophilic reagents. Their reactivity is dependent upon the extent of stabilization of the carbanion portion of the ylids. Highly reactive ylids have been prepared by the alkylation of diarylsulfides followed by treatment of the resulting sulfonium salts with a base such as phenyl lithium (14). The reactivity of β-carbonyl stabilized sulfonium ylids has been studied by Johnson and Amel (15). They found a phenacylid to be considerably less reactive than a simple alkylid. In addition, the ambident character of the phenacylid

resulted in products of C- and O-alkylation.

Figure III illustrates some reactions of dimethylsulfonium phenacylid (8) (15). Equation [3] illustrates the C-benzoylation of the phenacylid with benzoic anhydride to yield a highly stabilized ylid. The ambident character of a phenacylid was demonstrated by reaction of 8 with benzoyl chloride, eq. [4]. The intermediate vinyl sulfonium ion was unstable in the presence of chloride ion and demethylated to yield an enol benzoate. The phenacylid 8 could also be C-alkylated, though in low yield, using benzyl bromide, eq. [5]. Here again, the intermediate sulfonium ion was unstable in the presence of bromide ion and only the demethylated product was observed.

These reactions illustrated in Figure III were chosen as model reactions for the active sulfonium ylid (-)-5. The reaction conditions would, however, require some modification in order to ensure the isolation of optically active products.

First, for the C-acylation reaction, the reaction time would have to be shortened from 43 hours. The reported rate of racemization of (-)-5 at 25° in CH_2Cl_2 is 3.52×10^{-5} seconds^{-1} (9). The starting material would have therefore a half-life of loss of optical activity of ca. 5½ hours in the absence of any reactants. Even if the desired product were to racemize at the same rate as (-)-5 it would have been impossible to isolate optically active material in the reaction time reported.

The reaction time was shortened by treating (-)-5 with 15 equivalents benzoic anhydride in tetrahydrofuran (THF) at 25°. The progress of the reaction was followed by studying the rate of loss of optical activity with time. Figure IV is a plot of log $(\alpha_t - \alpha_\infty)$ versus

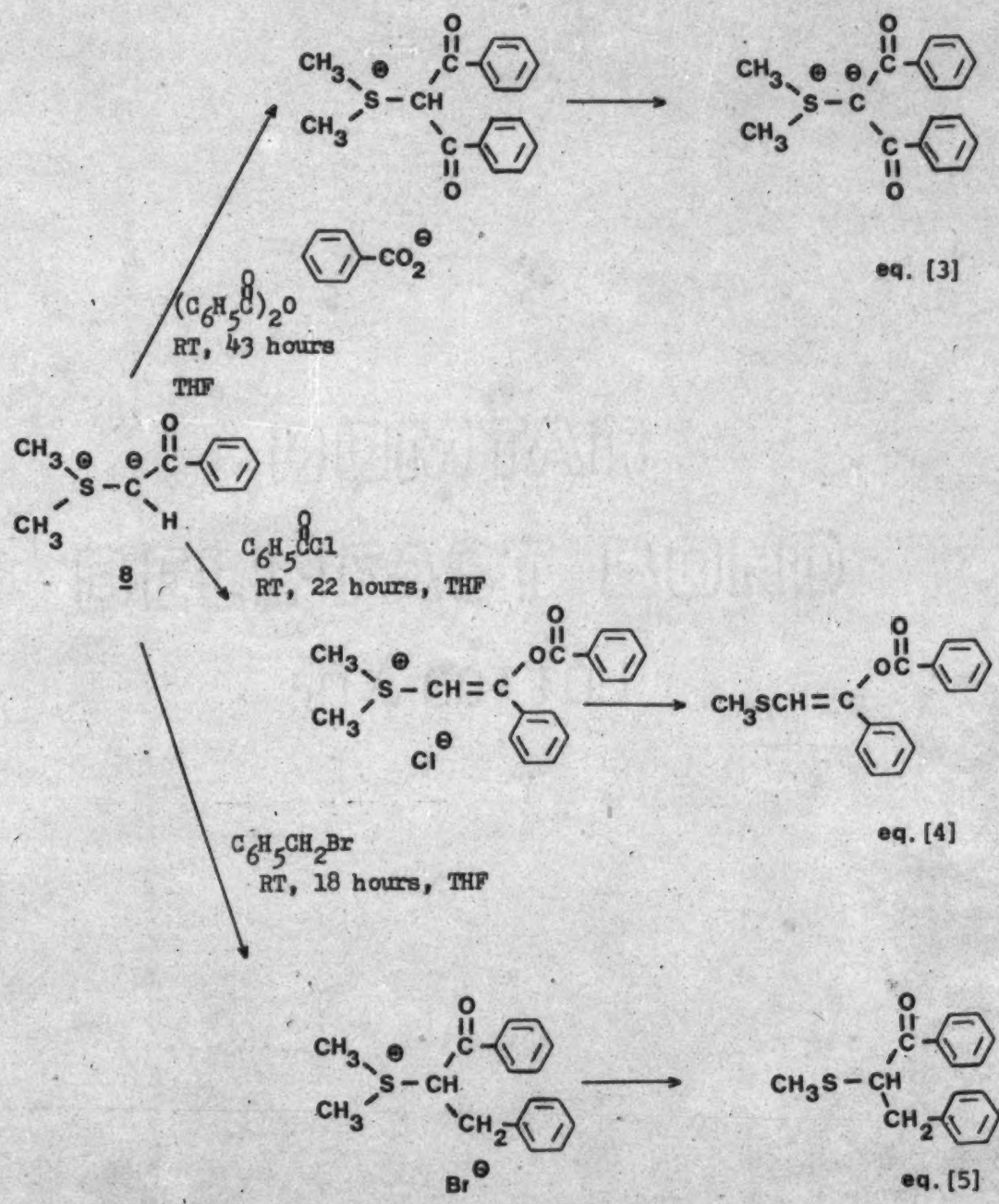


Figure III. Reactions of dimethylsulfonium phenacylid.

time for the early stages of the reaction. The technique for studying the loss of optical activity is described later in this chapter in the sections entitled Kinetic Results and Experimental. From Figure IV it is seen that after 2700 seconds of reaction, the curve resembles that for a first-order rate. From 0 to 2700 seconds there is an initial curvature indicating departure from first-order analysis. During this time, reaction is occuring to give a product of different optical rotatory power than that of the starting material. The reaction preparing the new ylid was therefore judged to be complete after 3000 seconds or 50 minutes. The loss of optical activity was followed to zero rotation. Figure V shows a plot of log $(\alpha_t - \alpha_\infty)$ versus time for this loss of optical activity after 2700 seconds. Upon complete loss of optical activity, the reaction mixture was diluted with chloroform and the mixture extracted several times with a 10% sodium hydroxide solution to destroy excess benzoic anhydride. The organic phase was washed with water, dried over magnesium sulfate and evaporated. The residual oil was titurated in Skellysolve B to yield crystalline (±)-ethylmethylsulfonium dibenzoylmethylid ((±)-9).

Optically active (-)-ethylmethylsulfonium dibenzoylmethylid ((-)-9) was prepared by treating (-)-5 with 15 equivalents benzoic anhydride in THF at room temperature for one hour. After a rapid workup, the residual oil was crystallized from chloroform-Skellysolve B solvent mixture to yield (-)-9, $[\alpha]_{546}^{RT}$ - 31.9° (c 1.38, benzene) in 51% isolated yield. In a similar manner, (-)-ethylmethylsulfonium acetylbenzoylmethylid ((-)-10), $[\alpha]_{546}^{RT}$ - 30.8° (c 0.766, benzene) was prepared by the reaction of 15 equivalents of acetic anhydride with one equivalent of (-)-5 in benzene at room temperature for 45 minutes.

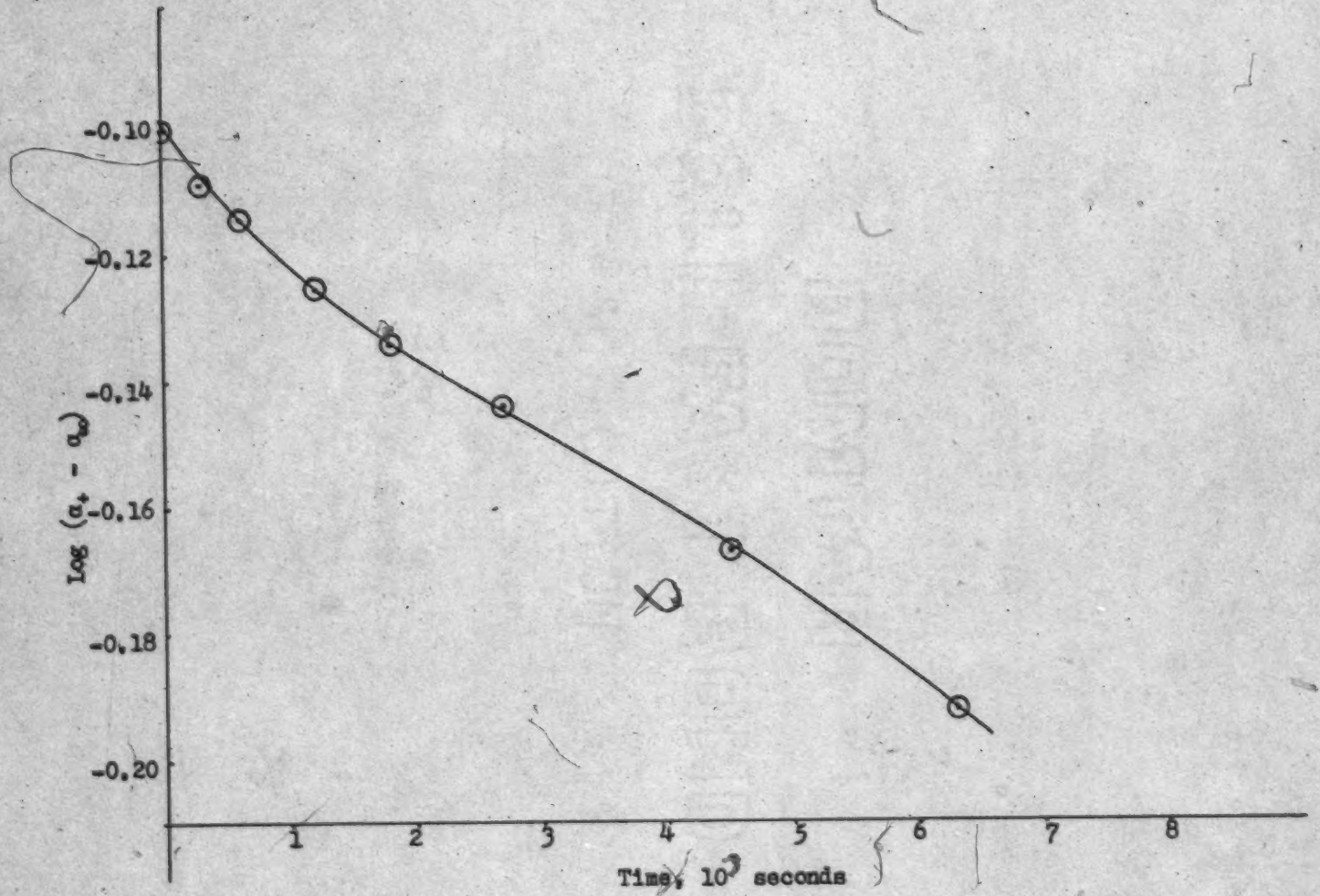


Figure IV. Log (α_t - α_∞) versus time for the racemization of (-)-ethylmethylsulfonium phenacylid in the presence of 15 eq. benzoic anhydride at 25° in THF.

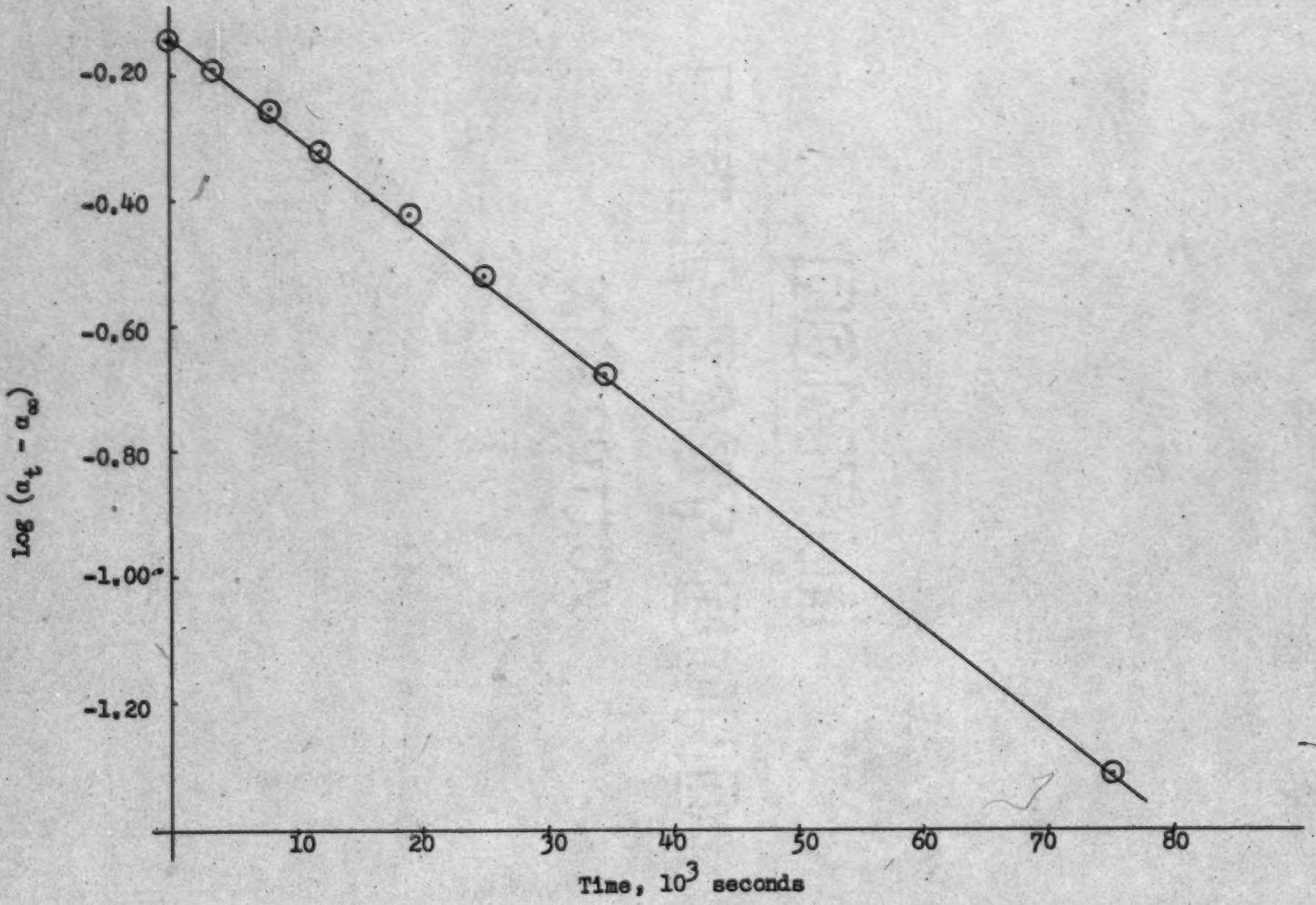


Figure V. Log ($\alpha_t - \alpha_\infty$) versus time for the racemization of benzoylated (-)-5 after 2700 seconds of reaction in THF at 25°.

The ylid (-)-5 was also treated with an equivalent of phenyl isocyanate in THF at room temperature for 15 minutes to yield after workup (-)-ethylmethylsulfonium benzoyl(N-phenylcarbamoyl)methylid ((-)-11), $[\alpha]^{RT}_{546}$ - 39.9° (c 0.727, benzene).

The N.M.R. spectra of (-)-9 were found to be invariant at temperatures of + 40°, - 20° and - 40°. However, the N.M.R. spectra of (-)-10 changed significantly upon the lowering of the temperature. At + 40° the acetyl-methyl signal was a sharp singlet at δ 2.14, whereas at - 60°, the absorption had broadened to a signal centered at δ 2.35. All other resonances remained essentially the same. The spectra of (-)-10 are illustrated in Figure VI. These temperature variable spectra are similar to those recorded by Nozaki, et al (7c) for dimethylsulfonium diacetylmethylid (4) and dimethylsulfonium acetylbenzoylmethylid (12). The interpretation of these spectral phenomena are presented later in this chapter.

Some physical constants and spectral properties of these new optically active sulfonium ylids are summarized in Table I. It is noted that the melting points reported in Table I for the active ylids are identical with those obtained for their racemates as reported in the experimental section. The identity of the melting points of the racemic and active isomers of the same ylid suggests that the ylids may have been racemizing during the heating process such that the melting points obtained are for racemic materials. Solid phase racemization was confirmed in that the active methylids 9, 10 and 11 were completely racemized after storage for one year at 5°.

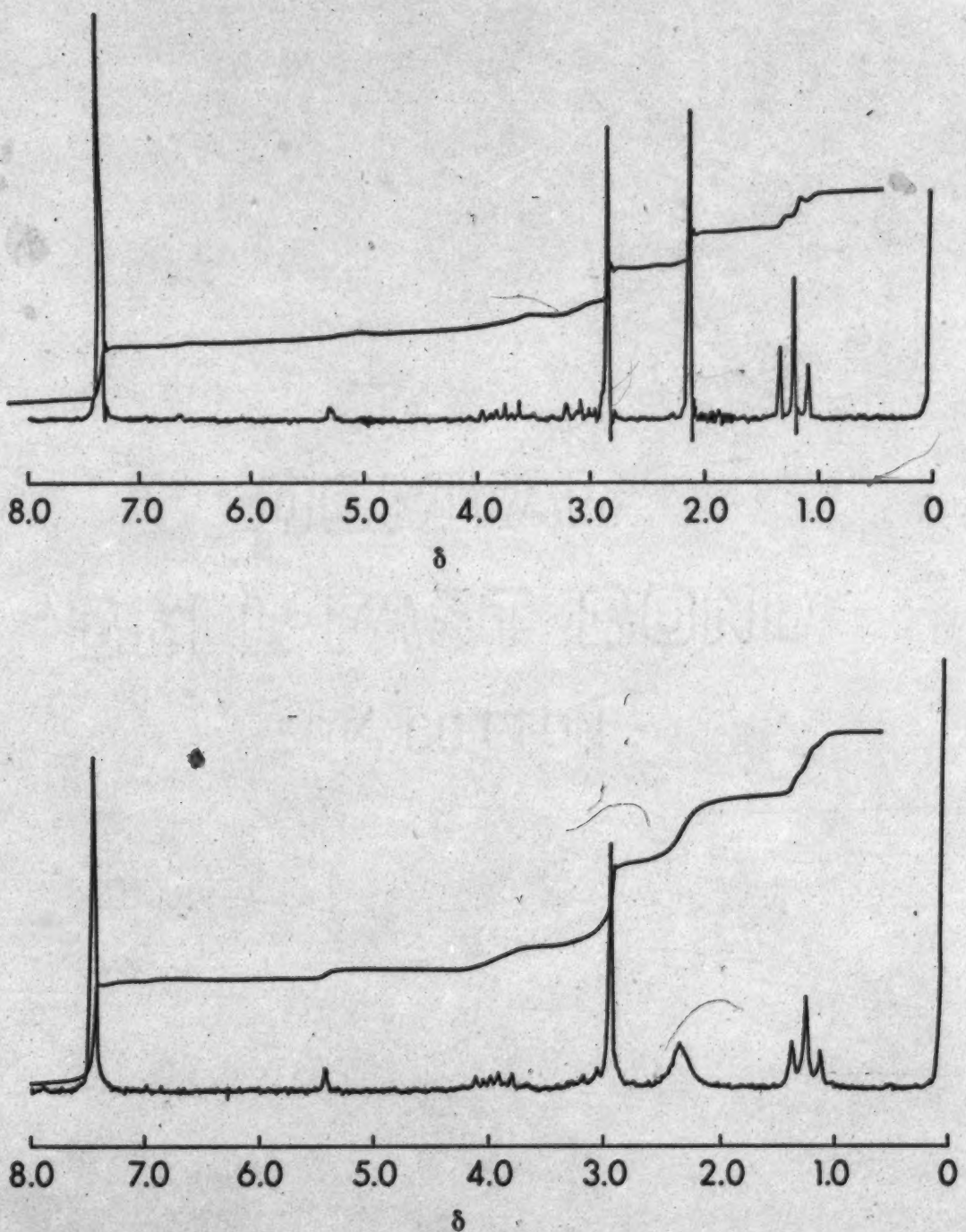
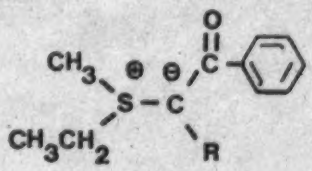


Figure VI. N.M.R. spectra of (-)-ethylmethylsulfonium acetylbenzoylmethylid ((-)-10) at + 40° (top) and - 60° (bottom) in CD_2Cl_2 with TMS as internal standard.

TABLE I

PROPERTIES OF SOME ETHYLMETHYLSULFONIUM METHYLIDS



Compound	R	M.p., °C	$[\alpha]_{546}^{RT}$ a	I.R.[b], cm^{-1}	N.M.R.[c], δ
(-)-2	C_6H_5CO	151 - 152	-31.9°	1570	3.92, 3.24
(-)-10	CH_3CO	98 - 99	-30.8°	1605	3.81, 3.06
(-)-11	C_6H_5NHCO	171 - 172	-39.9°	1635	3.97, 3.09
(-)-5	H	83 - 85	-216° [d]	1585	3.86, 3.00

a: c ca. 1, benzene.

b: As a nujol mull.

c: In $CDCl_3$, chemical shifts of diastereotopic protons.

d: λ 589 mμ, c ca. 0.5, benzene.

Equations [4] and [5] illustrate reactions in which the initially formed sulfonium halides were unstable and underwent demethylation reactions. In order to obtain products with the sulfonium center preserved, it was thought that a reactant containing a leaving group which would be non-nucleophilic would be appropriate. It was hoped that the ambident character of the nucleophilic portion of the ylid would lead to specifically O-alkylated and C-alkylated salts under the appropriate reaction conditions, however only O-alkylated materials were obtained.

When (-)-5 was treated with excess dimethyl sulfate in acetone for 30 minutes at room temperature, a vinyl sulfonium salt was obtained, Z-(+)-ethylmethyl-α-methoxy-β-styrylsulfonium methyl sulfate ((+)-13), $[\alpha]_{365}^{50}$ + 3.94° (c 5.2, methanol). The alkylation of 8 with trimethyloxonium tetrafluoroborate (Meerwin's Reagent) has been reported to yield a Z/E mixture of the analagous salt in a ratio of 94/6 (16). The assignment of the Z configuration to (+)-13 is based upon these results reported by Caserio, et al.

The ylid (±)-5 was treated with benzyl tosylate in THF at room temperature for twenty hours. The evaporation residue of the reaction mixture could not be crystallized from a methanol-ether solvent mixture. The N.M.R. spectrum of the oily product indicated the presence of two compounds while the Infrared spectrum showed a strong olefinic absorption at 1610 cm^{-1} and a weaker carbonyl absorption at 1690 cm^{-1}. To simplify the spectrum, the tosylate was converted to the perchlorate salt by anion exchange techniques. The perchlorate salt was crystallized as an 84/16 mixture of O-benzylated material 14 and ethylmethylphenacylsulfonium perchlorate (15). No resonances for C-alkylated

material were evident in the N.M.R. spectra of this perchlorate salt mixture.

Figure VII summarizes the reactions of (-)-ethylmethylsulfonium phenacylid which retained the sulfonium functionality of the initial starting material.

In order to obtain the active vinyl sulfonium salt 13 of higher specific rotation, the resolution of the salt via its DBT salt was attempted. Figure VIII outlines the procedure for the resolution of 13. Racemic 13 was dissolved in methanol, eluted through a Dowex 1 - X8 hydroxide exchange column and the eluate neutralized with an equimolar amount of HDBT. A diastereomeric salt mixture of ethylmethyl-2,2-dimethoxy-2-phenylethylsulfonium hydrogen 2(R),3(R)-dibenzoyltartrate (16) was obtained, an unexpected product of the Michael addition of the solvent across the vinyl sulfonium system. Repetition of this anion exchange reaction several times yielded varying amounts of the vinyl- and the Michael-addition sulfonium DBT salt, varying from pure vinyl 17 to pure Michael 16 or to mixtures of the two in the first crop from the fractional crystallization. The Michael and vinyl salts were easily distinguished as the N.M.R. spectra of the two were signficantly different. The experimental conditions could not be established such that either salt could be obtained exclusively with predictability. The Michael addition DBT salt was not converted back to a mixture of vinyl and Michael addition salts upon anion exchange from DBT to perchlorate. A base catalyzed Michael addition of methanol across the double bond of an analagous vinyl sulfonium salt has recently been reported by Stirling, et al (17).

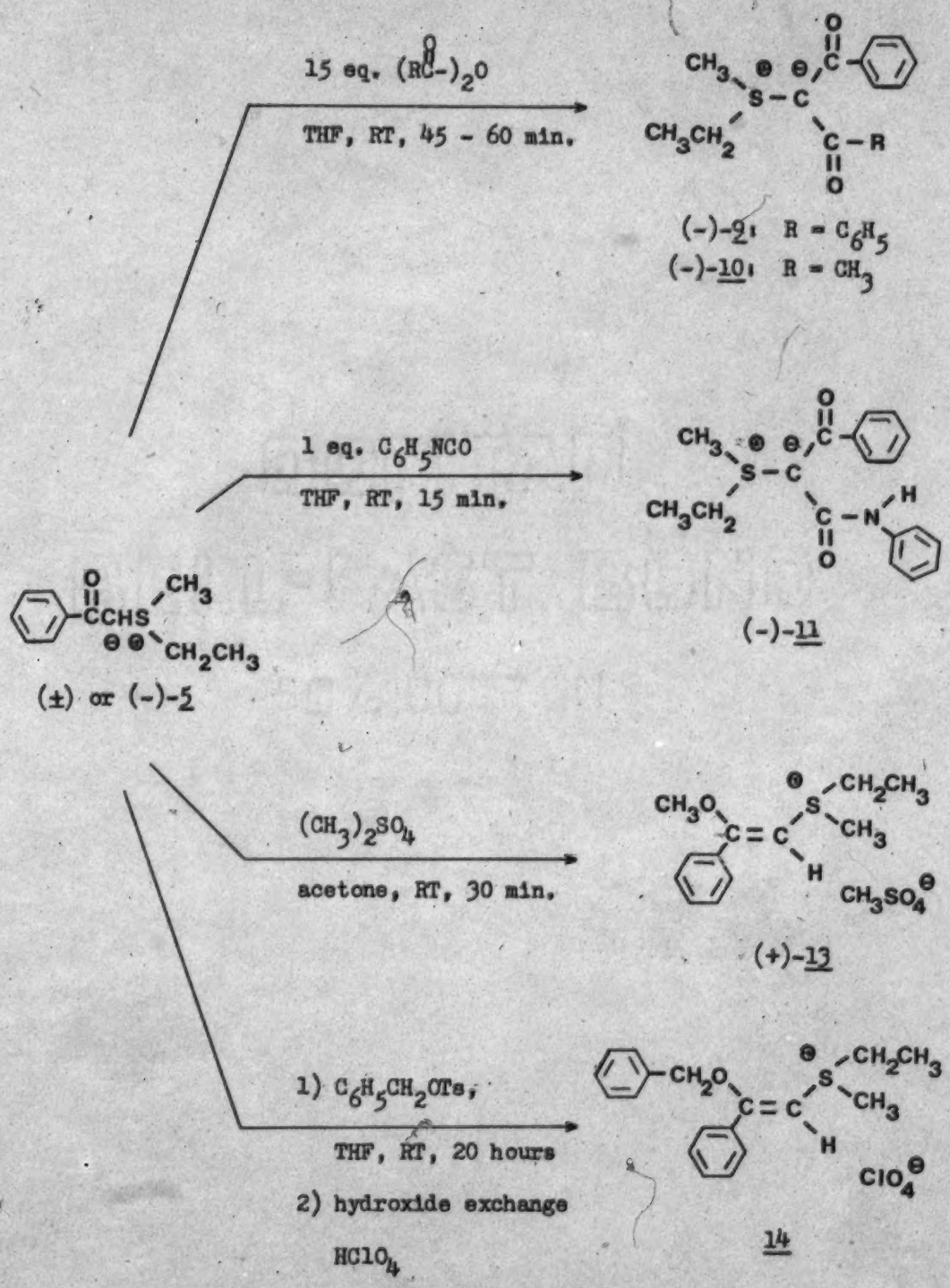


Figure VII. Some reactions of ethylmethylsulfonium phenacylid.

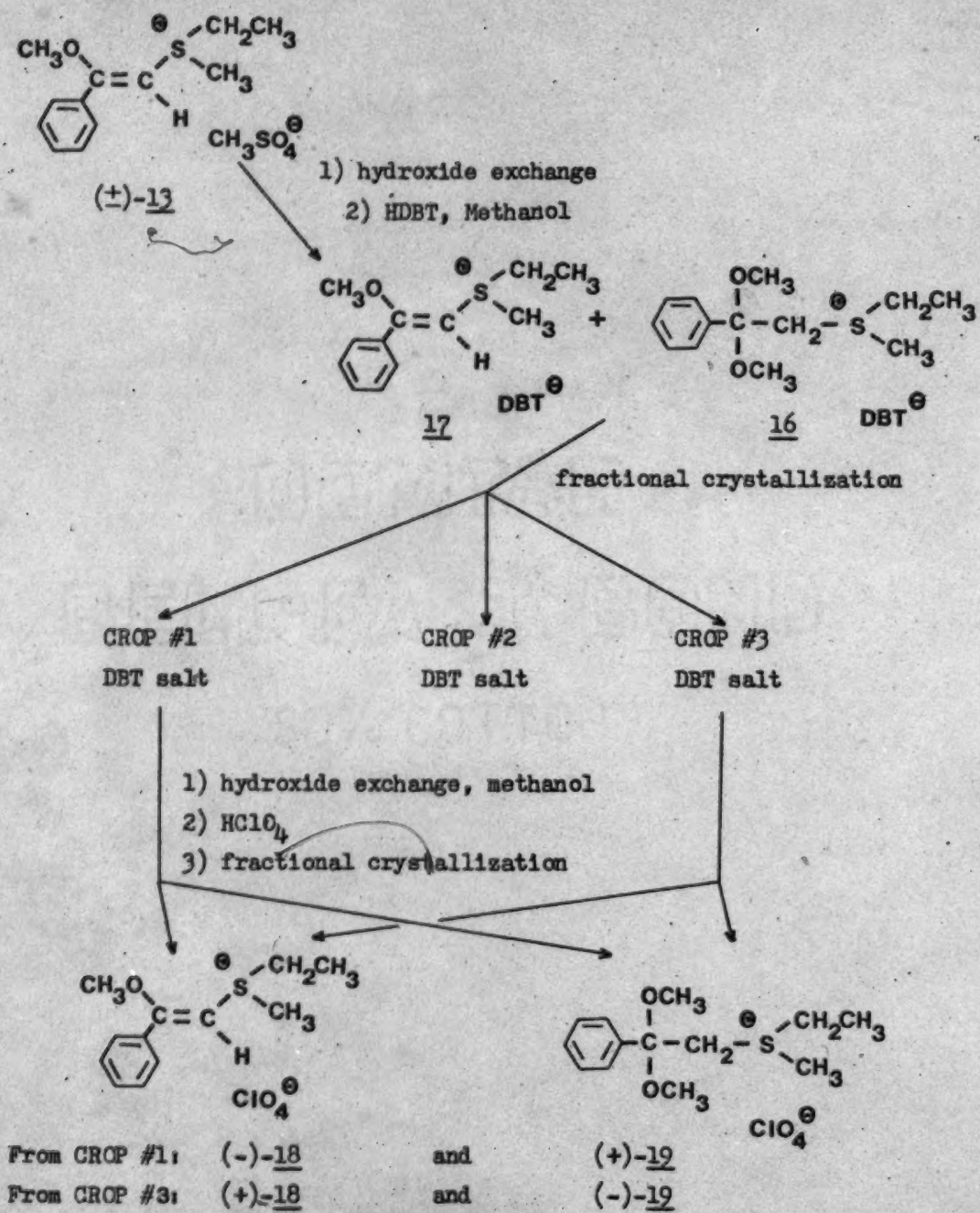


Figure VIII. Resolution of ethylmethyl-α-methoxy-β-styrylsulfonium methyl sulfate.

If then, for the first crop, the anion was exchanged from DBT to perchlorate, a mixture of (-)-ethylmethyl-α-methoxy-β-styryl-sulfonium perchlorate ((-)-18), $[\alpha]^{RT}_{365}$ - 8.80° (c 0.716, methanol) and (+)-ethylmethyl-2,2-dimethoxy-2-phenylethylsulfonium perchlorate ((+)-19), $[\alpha]^{RT}_{365}$ + 4.75° (c 0.642, methanol) were obtained which were easily separated by the fractional crystallization of the vinyl salt (-)-18 from a methanol-ether solvent mixture. From the mother liquor, the Michael-addition salt (+)-19 precipitated upon the addition of excess ether and the cooling of the resulting mixture at - 10°. In a similar manner the third crop of DBT salt from the resolution procedure was converted to a mixture of (+)-18, $[\alpha]^{RT}_{365}$ + 8.44° (c 0.842, methanol) and (-)-19, $[\alpha]^{RT}_{365}$ - 5.16° (c 1.14, methanol).

Thus, although the resolution of the racemic 13 was complicated by a side reaction leading to unexpected Michael-addition of solvent across the double bond, the vinyl perchorate eventually obtained from the resolution procedure was of higher molecular rotation, $[M]^{RT}_{365}$ - 27.2°, (c 0.716, methanol) than the material obtained by alkylation of (-)-5 with dimethyl sulfate, $[M]^{RT}_{365}$ + 12.6° (c 5.2, methanol). The yield of the vinyl salt was significantly reduced because of the unpredictable Michael-addition reaction. The Michael-addition product is a novel structure compared to previous optically active sulfonium salts resolved in these laboratories.

Kinetic Results

The rate of loss of optical activity, k_α, of the optically active sulfonium ylids and salts were studied by following the disappearance of optical activity with time. A Perkin-Elmer Model 141 Polarimeter was used with incident light of wavelengths of 546 mμ and 365 mμ as required. The reactions were followed either in a thermostated polarimeter cell (method I) or by using a sealed ampoule technique (method II) as described in the experimental section of this chapter. Rotations were obtained directly from the digital readout of the instrument, with an infinity measurement taken after 10 half-lives of reaction. The first order rate constants were calculated from eq. [6] where α_o is the initial rotation, α_t is the rotation at time t and α_∞ is the infinity reading. Reactions were usually followed to ca. 85% completion. Good first order rate constants were obtained. A straight line was obtained when log $(\alpha_t - \alpha_\infty)$ was plotted versus time. Typical examples of these rate studies using Method I and Method II are summarized in Table II and Table III, respectively. The corresponding plots of log $(\alpha_t - \alpha_\infty)$ versus time are illustrated in Figure IX and Figure X.

$$k_\alpha = \frac{2.303}{t} \log \frac{\alpha_o - \alpha_\infty}{\alpha_t - \alpha_\infty} \qquad [6]$$

TABLE II

RACEMIZATION OF (-)-ETHYLMETHYLSULFONIUM ACETYLBENZOYLMETHYLID (-)-10, 0.0325 M IN BENZENE AT 50°, METHOD I.

Time, sec.	α_t, °a	Log $(\alpha_t - \alpha_\infty)$	Log $\left(\frac{\alpha_o - \alpha_\infty}{\alpha_t - \alpha_\infty}\right)$	$10^3 k_\alpha$, $sec.^{-1}$
0	0.199	-0.7011		
60	0.187	-0.7282	0.0271	1.04
120	0.176	-0.7545	0.0534	1.02
200	0.160	-0.7959	0.0948	1.09
330	0.142	-0.8477	0.1466	1.02
450	0.123	-0.9101	0.2090	1.07
620	0.102	-0.9914	0.2903	1.08
780	0.088	-1.0555	0.3544	1.05
1080	0.062	-1.2076	0.5065	1.08
1520	0.038	-1.4202	0.7191	1.09
7200	0.000			

Average k_α ± average deviation = $(1.06 \pm 0.02) \times 10^{-3}$ $sec.^{-1}$

a: λ 546 mμ.

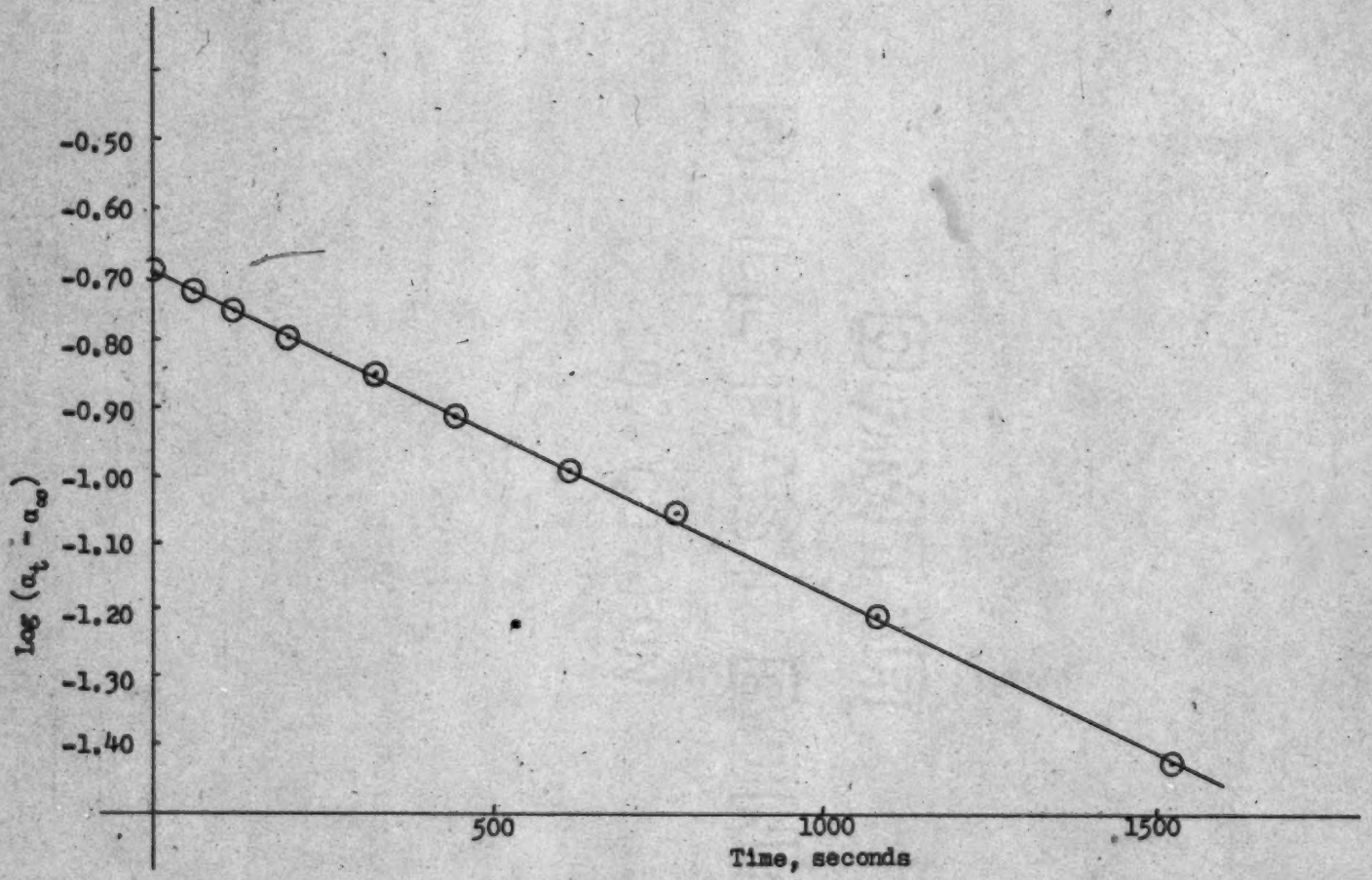


Figure IX. Log ($\alpha_t - \alpha_\infty$) versus time for the racemization of (-)-ethylmethylsulfonium acetylbenzoylmethylid, 0.0325 M in benzene at 50°, method I.

TABLE III

RACEMIZATION OF (+)-ETHYLMETHYL-2,2-DIMETHOXY-2-PHENYLETHYLSULFONIUM PERCHLORATE (+)-19, 0.0738 M IN METHANOL AT 25°, METHOD II.

Time, 10^3 sec.	α_t, ° [a]	$\text{Log}(\alpha_t - \alpha_\infty)$	$\text{Log}\left(\frac{\alpha_o - \alpha_\infty}{\alpha_t - \alpha_\infty}\right)$	$10^6 k_{rac.}$, sec.^{-1}
0	0.086	-1.0655		
95	0.073	-1.1367	0.0712	1.73
174	0.061	-1.2147	0.1492	1.98
431	0.041	-1.3872	0.3217	1.72
544	0.030	-1.5229	0.4574	1.94
611	0.026	-1.4850	0.5195	1.96
718	0.021	-1.6778	0.6123	1.96
1134	0.011	-1.9586	0.8931	1.82

Average $k_{rac.}$ ± average deviation = $(1.87 \pm 0.10) \times 10^{-6}$ sec.^{-1}

[a] λ 365 mμ.

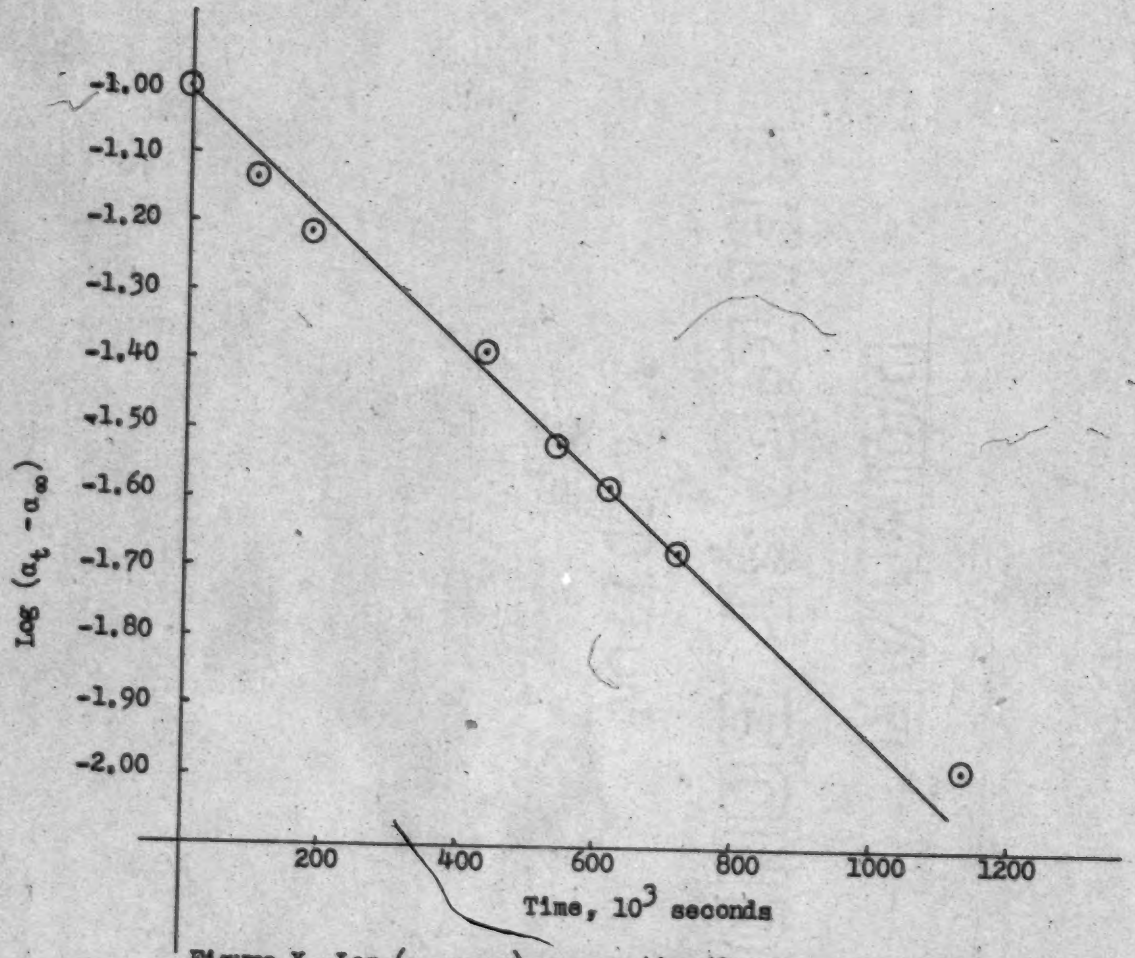
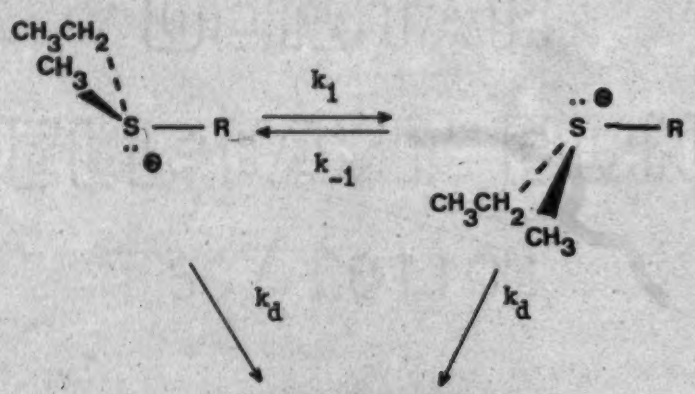


Figure X. Log ($\alpha_t - \alpha_\infty$) versus time for the racemization of ethylmethyl-2,2-dimethoxy-2-phenylethylsulfonium perchlorate, 0.0738 M in methanol at 25°, method II.

The rate constant k_1, the first order rate constant for the conversion of one enantiomer to the other by pyramidal inversion as illustrated in the scheme below, can be calculated from the rate of loss of optical activity k_α. As the N.M.R. spectra of the evaporation residues obtained after ten half-lives of loss of optical activity were superimposible upon those for racemic materials, k_d for these sulfonium ylids and salts were estimated to be very much smaller that k_α. Therefore to an excellent approximation, $k_{rac} = k_\alpha = 2k_1$.



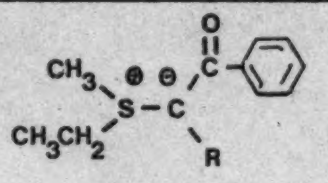
$$k_{rac} = 2k_1 = k_\alpha - k_d$$

Table IV summarizes the racemization rate constants, k_{rac}, for the sulfonium ylids studied in this chapter and Table V, those for the sulfonium salts. Values for related compounds are included for comparison.

The effect of temperature on the racemization of the sulfonium ylids and salts was determined using eq. [8], which was derived from the Arrhenius equation, eq. [7] (18). Substitution of the experimentally

TABLE IV

RATES OF RACEMIZATION OF SOME SULFONIUM YLIDS[a] IN BENZENE



Compound	R	[Ylid]	α_o, °	Temp., °	$10^5 k_{rac.}$, $sec.^{-1}$
(-)-2	C_6H_5CO	0.0463	0.147	50	55.5 ± 1.3
		0.0232	0.086	50	57.7 ± 1.1
		0.0463	0.108[b]	25	2.27 ± 0.07
(-)-10	CH_3CO	0.0325	0.194	50	106 ± 2
		0.066	0.109	50	107 ± 2
		0.0325	0.217	25	4.40 ± 0.07
(-)-11	C_6H_5NHCO	0.0232	0.290	50	79.1 ± 0.3
		0.0232	0.290[b]	25	3.20 ± 0.04
(-)-5[c]	H	0.018		50	39.7 ± 0.2
		0.021		25	1.67 ± 0.01

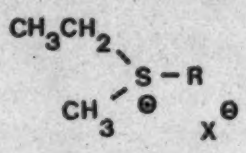
a: λ546 mμ, method I unless otherwise specified.

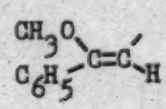
b: λ546 mμ, method II.

c: References (9) and (13).

TABLE V

RATES OF RACEMIZATION OF SOME ETHYLMETHYLSULFONIUM SALTS IN METHANOL[a]



Compound	R	$X^{\ominus}$	[Salt]	α_o, °	Temp, °	$10^5 k_{rac.}$, $sec.^{-1}$
(+)-13		CH_3SO_4	0.163[b]	0.179	50	1.93 ± 0.06
		"	0.127	0.071	70	29.7 ± 1.5[c]
(+)-18	"	ClO_4	0.072[b]	0.074	50	2.08 ± 0.17
		"	0.078	0.101	70	32.8 ± 2.0[c]
(-)-19	$C_6H_5C(OCH_3)_2CH_2$	ClO_4	0.112	0.158	50	5.26 ± 0.09
(+)-19	"	"	0.111	0.129	50	5.61 ± 0.14
	"	"	0.077	0.091	50	5.64 ± 0.02
	"	"	0.074	0.101	25	0.187 ± 0.010
(-)-15	$C_6H_5COCH_2$	ClO_4	0.020		50	0.373 ± 0.006[d]
	"	"	0.020		70	5.58 ± 0.18[d]
(-)	C_6H_5	ClO_4	0.030		50	2.88 ± 0.11[e]

a: λ365 mμ, method I unless otherwise specified.

b: Two equivalents of 2,6-lutidine added.

c: λ365 mμ, method II.

d: R. L. Tomilson and D. Darwish, references (9) and (13).

e: C. E. Scott and D. Darwish, reference (11).

$$k = Ae^{-Ea/RT} \qquad [7]$$

$$\log \frac{k_2}{k_1} = \frac{Ea}{2.303R}\left(\frac{T_2 - T_1}{T_1 T_2}\right) \qquad [8]$$

determined k_{rac} at the appropriate temperatures into equation [8] gives the energy of activation. For reactions in solution, the enthalpy of activation is given by eq. [9] (18).

$$\Delta H^{\ddagger} = Ea - RT \qquad [9]$$

The entropy of activation is calculated from the Eyring equation, eq. [10], where k_B is Boltzmann's constant, h is Plank's constant and κ is the transmission coefficient which for racemization is equal to one.

$$k = \kappa k_B T/h \cdot e^{\Delta S^{\ddagger}/R} \cdot e^{-\Delta H^{\ddagger}/RT} \qquad [10]$$

Thus at 50°

$$\Delta S^{\ddagger} = 4.576\left(\log k_{rac} - \log 12.83 + \frac{\Delta H^{\ddagger}}{1.478}\right)$$

The values calculated for the enthalpy and entropy of activation for the racemization of the sulfonium ylids and salts are listed in Table VI. The estimation of errors were calculated from the average deviations of the rate constants using the method described by Wiberg (19). As the average deviations for the rate constants for the salts were considerable, the activation parameters for these salts are at best approximations. The values for other ylids and salts are included in Table VI for immediate comparison.

TABLE VI

ACTIVATION PARAMETERS FOR THE RACEMIZATION OF SOME ETHYLMETHYL-SULFONIUM YLIDS AND SALTS AT 50° [a].

Ylid or Salt		Ea, kcal/mole	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, eu
$C_6H_5\overset{O}{\overset{\|}{C}}-\underset{}{C}-\overset{O}{\overset{\|}{C}}C_6H_5$		24.5 ± 0.5	23.9 ± 0.5	0.4 ± 1.5
$C_6H_5\overset{O}{\overset{\|}{C}}-\underset{}{C}-\overset{O}{\overset{\|}{C}}CH_3$		24.3 ± 0.3	23.7 ± 0.3	0.1 ± 0.9
$C_6H_5\overset{O}{\overset{\|}{C}}-\underset{}{C}-\overset{O}{\overset{\|}{C}}NHC_6H_5$		24.5 ± 0.2	23.9 ± 0.2	1.1 ± 0.6
$C_6H_5\overset{O}{\overset{\|}{C}}-\underset{}{C}-H$ [b]			23.6 ± 0.2	-1.1 ± 0.5
CH_3O, C_6H_5 $C=C'$, H	CH_3SO_4	30.1 ± 0.5	29.5 ± 0.5	11 ± 1.6
"	ClO_4	30.4 ± 1.8	29.8 ± 1.8	12 ± 5.7
$C_6H_5C(OCH_3)_2CH_2-$	ClO_4	26.1 ± 0.8	25.5 ± 0.8	0.8 ± 2.6
$C_6H_5\overset{O}{\overset{\|}{C}}CH_2-$	ClO_4 [b]		29.0 ± 0.5	4.4 ± 0.6
C_6H_5-	ClO_4 [c]		27.5 ± 0.4	4.1 ± 1.2

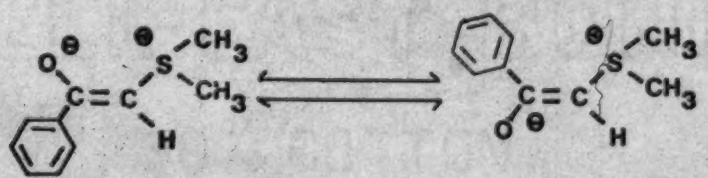
a: Ylids in benzene, salts in methanol.

b: R. L. Tomilson and D. Darwish, references (9) and (13).

c: C. E. Scott and D. Darwish, reference (11).

Discussion

Several reports of N.M.R. temperature dependent exchange processes in sulfonium ylids have appeared. The line widths and chemical shifts of the methine proton resonance of dimethylsulfonium phenacylid were temperature dependent (20,21). It was suggested that this may reflect a C—C rotational process interconverting Z and E conformers. However, this spectral phenomena has since been shown to result from an intermolecular exchange reaction between ylid and trace amounts of water and other proton acids (16). Indeed, the N.M.R. spectra of anhydrous 8 in ethanol-free $CDCl_3$ were found to be temperature invariant over the temperature range - 30° to 100°. It was concluded that C—C rotation was rapid on the N.M.R. time scale.



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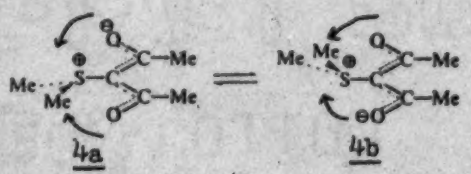
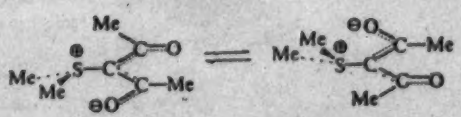
The N.M.R. spectrum of dimethylsulfonium diacetylmethylid (4) showed magnetic equivalence of the two acetyl-methyl groups at room temperature. However at - 60° , the C-methyl signals were split into a 1:1 doublet with the critical temperature being ca. -25°. The spectral resonances of dimethylsulfonium acetylbenzoylmethylid (12) and those of (-)-10, the optically active ethylmethyl analogue, showed similar temperature dependence with coalescence occuring ca. - 60°. Nozaki, et al postulated that two processes would account for these observations: hindered rotation around the S—C bond or inversion of configuration at the sulfur atom, 4a ⇄ 4b, both of which would be slowed down upon cooling.

A third alternative explanation of the effect, exchange between 4c and 4c', was considered less likely as it would require the simultaneous inversion at the sulfur atom and internal rotation of two C—C bonds. They had confirmed the pyramid structure of the sulfur atom in ylids by the non-equivalence of the prochiral protons of a methylene group attached to the sulfur. Having no estimate of the rate of the racemization process and the earlier failure to resolve methylphenylsulfonium p-iodophenacylid lead them to prefer the latter alternative for the kinetic process involved. The isolation of optically active (-)-ethylmethylsulfonium acetylbenzoylmethylid (-)-10 and the kinetic study of the ylid indicates that the temperature dependence observed was related to hindered rotation about the S—C bond and not to pyramidal inversion.



4a 4b



4c 4c'

Three nondestructive processes must be considered for the racemization of these sulfonium ylids. The first is carbon-sulfur bond fission to form a carbene and ethyl methyl sulfide, which could recombine to give racemic ylid. This process has been considered and ruled out by Nozaki, et al (6) for methylphenylsulfonium phenacylid. Heating this ylid in the presence of sulfides other than phenyl methyl sulfide produced no sulfide exchange. Furthermore, no exchange was

observed in the formation of this ylid from the corresponding sulfonium salt in the presence of a foreign sulfide. Racemization via associated species can be ruled out since the kinetic data reveal that the rate constants are independent of ylid concentration. Nozaki did find that mixtures of certain ylids underwent ylid-exchange possibly via associated species to the extent of 8% in refluxing benzene. From the kinetic analysis, the ylid (-)-10 at the higher temperature of ca. 80° would have a half-life of ca. 26 seconds. Clearly only pyramidal inversion can account for the racemization of these sulfonium ylids.

Factors affecting the rate of pyramidal inversion in molecules containing a trivalent atom (N, S^+, O^+, P, As, etc.) have been reviewed by Bent (23), Lehn (24) and Mislow (25). The major factors that influence the magnitude of an inversion barrier are steric effects, conjugation, angular constraints and electronic effects.

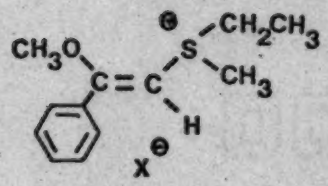
Steric acceleration of the pyramidal inversion reaction in sulfonium salts has been demonstrated by Darwish, et al (10,11). In aryl sulfonium salts, the substitution of an aryl group for a primary alkyl group caused an ca. 10-fold rate enhancement in the pyramidal inversion reaction. An analagous steric effect, phenyl versus ethyl, probably accounted for Nozaki's failure to obtain optically active methylphenylsulfonium p-iodophenacylid. Although the magnitude of the rate enhancement for aryl substitution of a primary alkyl group may be different for sulfonium phenacylids than for sulfonium salts, a sizeable effect is still anticipated. Electronically, it was reasoned that the sulfur pyramid of a diacylmethylid may have been forced into a more planar configuration because of coulombic stabilization between the electron-rich oxygen atoms and the positive sulfur as illustrated in

conformations 4a and 4b, thereby lowering the barrier to pyramidal inversion.' However, it is evident from the present work that the steric and electronic effect of a diacylmethylid group compared to a phenacylid group is not so great as to prevent the isolation of the optically active ethylmethylsulfonium diacylmethylids.

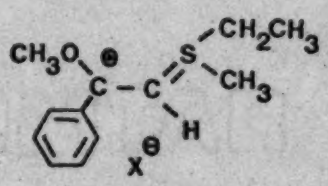
The ylid (-)-5 has been found to racemize 200 times faster than its corresponding perchlorate salt (-)-15 (9). Darwish and Tomilson have suggested this faster racemization of the ylid was due to the phenacylid group being more electropositive than a phenacyl group. As a result, the lone pair of electrons on the sulfur atom of the ylid were expected to have greater p-character and the ylid to be more nearly planar than the salt. Since the transition state for pyramidal inversion is planar, it was reasoned that the energy of activation should be correspondingly less for the ylid than the salt. An alternative explanation for the faster racemization of the ylid was that p-d π-bonding might have been better at the transition state for the ylid than for the ground state whereas no such stabilization of the transition state was possible for the salt. By a similar reasoning, a slower racemization of the vinyl salt (+)-13 compared with that of its ylid precursor (-)-5 was anticipated. As a phenacylid group is anticipated to be more electropositive than a vinyl group, the ylid should be more planar and have a lower activation energy. Furthermore, O-alkylation removes the extensive p-d π-bonding postulated to accelerate the pyramidal inversion process.

The five-fold increase in the rate of racemization of the vinyl salt (+)-13 compared with that of (-)-15 may be due to small resonance contributions such as 13b and 13c slightly favouring the planar

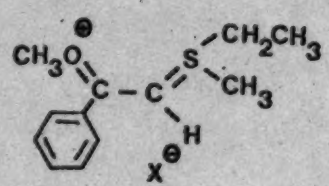
transition state over the ground state in the vinyl salt. On the other hand, the vinyl substituent might cause larger nonbonded interactions than a phenacyl substituent thereby accelerating the rate of racemization. A steric acceleration is certainly occuring for the Michael salt 19 compared with the phenacyl salt 15 as evidenced by the 14-fold rate enhancement upon ketalization of the phenacyl substituent.



13a



13b



13c

Experimental

Physical Measurements:

All melting points were obtained using a Hershberg type melting point apparatus with a set of Anschutz thermometers. All values are uncorrected.

Nuclear Magnetic Resonance spectra were recorded using Varian Analytical N.M.R. Spectrometers, Models A-60 and A-56-60. The latter model was also used for low temperature runs. Chemical shifts are reported in δ units from internal tetramethylsilane (TMS).

Infrared spectra were recorded on a Perkin-Elmer Grating Infrared Spectrometer Model 421.

Optical rotation measurements were obtained using a Perkin-Elmer Polarimeter Model 141.

Elemental analyses were performed by Mrs. D. Mahlow and Mrs. A. Dunn.

Solvents for Kinetic Experiments:

Anhydrous Methanol

Anhydrous methanol was prepared from commercially available methyl hydrate by treatment with magnesium methoxide and distillation as described by Fieser (26).

Benzene

Shawinigan Reagent Grade Benzene was purified according to the method of Fieser (26) by treatment with concentrated sulfuric acid. The treated solvent was distilled from calcium hydride.

Reagents and Materials:

Organic solvents were removed on a rotary evaporator under reduced pressure.

2,6-Lutidine

2,6-Lutidine was kindly supplied by M. A. Armour. It had been purified as follows. Eastman practical grade 2,6-lutidine was dried over potassium hydroxide for several days, followed by refluxing and distillation from barium oxide as described by Fieser for the preparation of anhydrous pyridine (26). The center cut was treated with boron trifluoride and distilled as described by Brown, et al (27).

Ethyl Methyl Sulfide

Eastman Kodak ethyl methyl sulfide was used directly without purification.

Phenacyl Bromide

Eastman Kodak phenacyl bromide was used directly without purification.

Preparation and Use of Hydroxide Exchange Columns

A 25 x 450 mm. column of Dowex 1-X8 exchange resin, 50 - 100 mesh, in its chloride form, was continuously washed with 5% sodium hydroxide solution until all the chloride ions had been eluted (negative silver chloride test). The column was then washed with technical grade methanol until the eluate tested neutral. Reagent grade methanol was used to elute samples for anion exchange. The sulfonium hydroxide eluates were

collected and immediately neutralized with a dilute solution of the required acid.

Precautions were necessary in the preparation of the perchlorate salts: excess acid was avoided; evaporation of the neutralized eluate was not continued to dryness as there was the danger of an explosion; and oily salts were not induced to crystallize by scratching or tituration.

(±)-Ethylmethylsulfonium Phenacylid ((±)-5)

Ethylmethylsulfonium phenacylid was prepared in a manner similar to that described by Darwish and Tomilson (9). Phenacyl bromide (23.1 g, 0.116 mole) and ethyl methyl sulfide (8.8 g, 0.116 mole) were dissolved in 50 ml. acetone and the mixture let stand in the dark at room temperature for 2½ hours. A large excess of ether was added to the acetone solution and the mixture cooled overnight at - 10°.

The supernatant liquid was decanted from the oily precipitated bromide (±)6. The crude bromide was treated with 200 ml. of 5% sodium hydroxide solution at 5° for 20 minutes. The solution was extracted several times with chloroform, the combined extracts washed with water, dried over magnesium sulfate and the chloroform removed. The yellow residual oil was crystallized from benzene-Skellysolve B solvent mixture to yield 12.3 g (0.0635 mole, 55%) (±)5: m.p. 83° (reported 83 - 85° (9)); N.M.R. ($CDCl_3$), δ 7.85 (m, 2H), 7.43 (m, 3H), 4.23 (m, 1H), 3.86 (m, 1H), 3.00 (m, 1H), 2.90 (s, 3H), 1.26 (t, J = 7.0 cps, 3H); Infrared (nujol), 1585 (m), 1510 (s), 1455 (s), 1200 (m), 1045 (m), 850 (s) cm^{-1}.

(-)-2(R),3(R)-Dibenzoyltartaric Acid Monohydrate (HDBT)

(-)-2(R),3(R)-Dibenzoyltartaric acid monohydrate was prepared according to the method described by Butler (12).

(-)-Ethylmethylphenacylsulfonium Hydrogen 2(R),3(R)-Dibenzoyltartrate ((-)-7)

To a methanol solution of 5 g (0.0258 mole) (±)-5, was added 9.7 g (0.0258 mole) HDBT. After stirring to effect solution, the mixture was cooled at 5° overnight. The resulting crystals were collected by filtration, ground to a powder, dissolved in a minimum volume of methanol at room temperature and recrystallized at 5°. Three further recrystallizations by this technique yielded, as large prisms, 1.8 g (3.26 mmole, 12.6%) (-)-7: $[\alpha]_{589}^{RT}$ - 90.2° (c 0.564, methanol) (reported $[\alpha]_{589}^{RT}$ - 88.2° (13)); N.M.R. (DMSO-d_6), δ 8.15 - 7.15 (m, 17H), 5.67 (s, 2H), 3.41 (q, J = 7.0 cps, 2H), 2.94 (s, 3H), 1.36 (t, J = 7.0 cps, 3H).

(-)-Ethylmethylsulfonium Phenacylid ((-)-5)

A quantity of 5 g (9.07 mmole) (-)-7, $[\alpha]_{589}^{RT}$ - 90.2° (c 0.564, methanol), was dissolved in 60 ml. of 10% sodium hydroxide solution and the mixture stirred at 0° for ½ hour. The reaction mixture was extracted with chloroform, the extracts washed with water, dried over magnesium sulfate and the chloroform removed on a rotary evaporator. The residual yellow oil was crystallized from benzene-Skellysolve B solvent mixture to yield 1.5 g (7.74 mmole, 85%) (-)-5: m.p. 83°; $[\alpha]_{589}^{RT}$ - 216 (c 0.419, benzene) (reported $[\alpha]_{589}^{RT}$ - 137 (c 0.487,

benzene (9)). The N.M.R. and Infrared spectra were superimposible with those of racemic material. In subsequent experiments, material having specific rotations of ca. 180° were used.

Racemization of (-)-Ethylmethylsulfonium Phenacylid in the Presence of 15 Equivalents of Benzoic Anhydride

A 0.148 g (0.764 mmole) quantity of (-)-5 and benzoic anhydride (2.59 g, 11.5 mmole) were weighed into a 10 ml. tared volumetric flask and THF added to the mark. The rate of loss of optical activity was studied by Method I described later in this section. Table VII presents the data for this racemization. It was evident from these data that optically active (-)-ethylmethylsulfonium dibenzoylmethylid could be isolated if the reaction was quenched in one hour. Assuming benzoylation to be complete after ca. 2700 seconds, an approximate rate constant for the loss of optical activity was calculated to be $(3.33 \pm 0.20) \times 10^{-5}$ seconds^{-1} at 25° in THF. The ylid had therefore a half-life of activity of ca. 6 hours under the preparative conditions. After racemization was complete, the crude ylid was isolated from the reaction mixture as described in the immediately following synthesis. The crude residual oil was titurated in Skellysolve B and filtered after crystallizaiton to yield 0.171 g (0.573 mmole, 75%) (±)-ethylmethylsulfonium dibenzoylmethylid ((±)-9), m.p. 150 - 151°.

(±)- Ethylmethylsulfonium Dibenzoylmethylid ((±)-9)

Ylid (-)-5 (1.163 g, 6.00 mmole) and benzoic anhydride (20.3 g, 91.0 mmole) were dissolved in 15 ml. THF and the mixture stirred at

TABLE VII

RACEMIZATION OF (-)-ETHYLMETHYLSULFONIUM PHENACYLID IN THE PRESENCE OF 15 EQUIVALENTS OF BENZOIC ANHYDRIDE AT 25° IN THF.

Time, 10^2 sec.	Time[a], 10^2 sec.	α_t,[b]	Log $(\alpha_t - \alpha_\infty)$	Log $\left(\frac{\alpha_o - \alpha_\infty}{\alpha_t - \alpha_\infty}\right)$[a]	$10^5 k_1$[a], $sec.^{-1}$
0		0.793	-0.1007		
3		0.778	-0.1090		
6		0.769	-0.1141		
12		0.749	-0.1255		
18		0.734	-0.1343		
27	0	0.717	-0.1445		
63	36	0.642	-0.19[illegible]	0.0480	2.94
108	81	0.553	-0.2573	0.1128	3.07
150	123	0.476	-0.3224	0.1779	3.21
218	191	0.372	-0.4295	0.2850	3.42
279	252	0.299	-0.5243	0.3798	3.47
376	349	0.208	-0.6819	0.5374	3.55
779	752	0.048	-1.3188	1.1743	3.60
931	904	0.033	-1.4815	1.3370	3.41
		0.000			

Average k_1 ± average deviation = $(3.33 \pm 0.20) \times 10^{-5}$ $seconds^{-1}$

a: Time of 2700 seconds taken as t_o for the calculation of the rate constant for racemization of the benzoylated product.

b: λ 546 mμ.

room temperature for 4 hours. The mixture was diluted with chloroform and the resulting solution extracted with dilute sodium hydroxide several times. The combined aqueous layers were extracted with chloroform. The organic layers were washed with water, dried over magnesium sulfate and evaporated. The residual oil was crystallized from chloroform-Skellysolve B solvent mixture to yield 1.132 g (3.80 mmole, 63.4%) (±)-9; m.p. 153 - 154°; N.M.R. ($CDCl_3$), δ 7.02 (m, 10H), 3.92 (m, 1H), 3.24 (m, 1H), 2.95 (s, 3H), 1.34 (t, J = 7.0 cps, 3H); Infrared (nujol), 1570 (s), 1545 (s), 1015 (m), 955 (m) cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08; S, 10.74. Found: C, 72.26, 72.48; H, 6.23, 5.89; S, 10.85, 10.67.

(-)-Ethylmethylsulfonium Dibenzoylmethylid ((-)-9)

A 1.16 g quantity (5.97 mmole) of (-)-5 and benzoic anhydride (20.3 g, 91.0 mmole) were dissolved in 15 ml. of THF and stirred at room temperature for one hour. The workup procedure was the same as that for the racemic material, yielding 0.924 g (3.10 mmole, 51%) (-)-9; m.p. 151 - 152°; $[\alpha]^{RT}_{546}$ - 31.9° (c 1.38, benzene). The N.M.R. and Infrared spectra were identical with those of the racemate.

Anal. Calcd. for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08; S, 10.74. Found: C, 72.08, 71.77; H, 6.22, 5.96; S, 10.43, 10.34.

(±)-Ethylmethylsulfonium Acetylbenzoylmethylid ((±)-10)

A 1.17 g quantity (6.02 mmole) of (±)-5 was dissolved in 10 ml. of benzene. Freshly distilled acetic anhydride (8.5 ml., 90 mmole) was added and the reaction mixture stirred overnight at room temperature. 50 ml. of a 20% sodium hydroxide solution was added and the mixture

stirred for 30 minutes then extracted with chloroform several times. The combined organic extracts were washed with water, dried over magnesium sulfate and evaporated. The oily residue was crystallized from chloroform-Skellysolve B solvent mixture to yield 1.20 g (5.08 mmole, 85%) (±)-10; m.p. 98 - 99°; N.M.R. ($CDCl_3$), δ 7.33 (s, 5H), 3.81 (m, 1H), 3.06 (m, 1H), 2.86 (s, 3H), 2.14 (s, 3H), 1.24 (t, J = 7.0 cps, 3H); Infrared (nujol), 1605 (s), 1560 (s), 1020 (m), 960 (m), 710 (m) cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82; S, 13.57. Found: C, 65.69, 66.10; H, 6.83, 6.76; S, 13.50, 13.44.

(-)-Ethylmethylsulfonium Acetylbenzoylmethylid ((-)-10)

A 1.26 g quantity of (-)-5 (6.47 mmole) was dissolved in 10 ml. of THF. Freshly distilled acetic anhydride (10 ml., 106 mmole) was added and the solution stirred at room temperature for 45 minutes. 100 ml. of a 10% sodium hydroxide solution was added and the resulting mixture stirred for 20 minutes to decompose the excess anhydride. The reaction solution was extracted with methylene chloride several times and the extracts dried over magnesium sulfate and evaporated. The residual oil was crystallized from benzene-Skellysolve B solvent mixture to yield 1.31 g (5.55 mmole, 85%) (-)-10; m.p. 98 - 99°; $[\alpha]_{546}^{RT}$ - 30.8° (c 0.77, benzene). The N.M.R. and Infrared spectra were identical with those of the racemic material.

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82; S, 13.57. Found: C, 65.76, 66.14; H, 6.72, 7.06; S, 13.54, 13.97.

(±)-Ethylmethylsulfonium Benzoyl(N-phenylcarbamoyl)methylid ((±)-11)

A 1.17 g (6.02 mmole) quantity of (±)-5 and phenyl isocyanate (0.72 g, 6.05 mmole) were dissolved in 25 ml. THF and the solution stirred for 2 hours at room temperature. Excess phenyl isocyanate was destroyed by the addition of 0.1 ml. 95% ethanol. The solvent was removed and the residual oil crystallized from chloroform-Skellysolve B solvent mixture to yield 1.80 g (5.77 mmole, 96%) (±)-11; m.p. 171 - 172°; N.M.R. ($CDCl_3$), δ 12.32 (s, 1H), 7.34 (m, 10H), 3.97 (m, 1H), 3.09 (m, 1H), 2.89 (s, 3H), 1.20 (t, J = 7.0 cps, 3H); Infrared (nujol), 2200 - 4000 (broad), 1635 (s), 1595 (s), 1520 (s), 1055 (m)cm^{-1}.

Anal. Calcd. for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47; S, 10.23. Found: C, 69.26, 68.88; H, 6.33, 6.26; N, 4.56, 4.45; S, 10.31, 10.20.

(-)-Ethylmethylsulfonium Benzoyl(N-phenylcarbamoyl)methylid ((-)-11)

A quantity of 2.09 g (10.8 mmole) of (-)-5 and phenyl isocyanate (1.3 g, 10.9 mmole) were dissolved in 25 ml. of THF and the solution stirred at room temperature for 15 minutes. The workup procedure was identical to that for the racemic material yielding 3.03 g (9.67 mmole, 89.6%) (-)-11; m.p. 171 - 172°; $[\alpha]_{546}^{RT}$ - 39.9° (c 0.73, benzene). The N.M.R. and Infrared spectra were identical with those of racemic material.

Anal. Calcd. for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47; S, 10.23. Found: C, 68.79, 69.11; H, 6.37, 6.20; N, 4.42, 4.45; S, 10.49, 10.38.

Z-(±)-Ethylmethyl-α-methoxy-β-styrylsulfonium Methyl Sulfate ((±)-13)

A quantity of 5 g (25.8 mmole) (±)-5 and dimethyl sulfate (5 g, 39.7 mmole) were dissolved in 50 ml. of acetone and the solution let stand at room temperature for one hour. Ether was added to the reaction mixture to the cloud point and the mixture cooled at - 5°. The resulting oil was induced to crystallize by scratching the sides of the flask to yield after filtering 7.4 g crude material. This was recrystallized from methanol-ether solvent mixture to yield 5.4 g (16.9 mmole, 65%) (±)-13; m.p. 103°, N.M.R. ($CDCl_3$), δ 7.51 (s, 5H), 6.00 (s, 1H), 3.74 (s, 1H), 3.62 (s, 3H), 3.62 (q, J = 7.0 cps, 2H), 3.13 (s, 3H), 1.42 (t, J = 7.0 cps, 3H); Infrared ($CHCl_3$); 2990 (s), 1608 (s), 1572 (m), 1490 (m), 1452 (s), 1210 (s), 610 (m), 575 (m) cm^{-1}.

Anal. Calcd. for $C_{13}H_{20}O_5S_2$: C, 48.73; H, 6.29; S, 20.01. Found: C, 48.60, 48.95; H, 6.18, 6.23; S, 20,26, 20,28.

Z-(+)-Ethylmethyl-α-methoxy-β-styrylsulfonium Methyl Sulfate ((+)-13)

A 2.2 g (11.3 mmole) quantity of (-)-5 and dimethyl sulfate (2.2 g, 17.5 mmole) were dissolved in 30 ml. acetone and the solution stirred for 30 minutes at room temperature. Ether was added to the reaction mixture to the cloud point and the mixture cooled at - 5°. The crystalline product was filtered yielding 0.90 g (2.8 mmole, 25%) (+)-13; m.p. 101 - 102°; $[\alpha]_{365}^{RT}$ + 3.94° (c 5.2, methanol). The N.M.R. and Infrared spectra were identical with those for the racemate.

Anal. Calcd. for $C_{13}H_{20}O_5S_2$: C, 48.73; H, 6.29; S, 20.01. Found: C, 48.77, 48.96; H, 6.26, 5.90; S, 20.20, 19.78.

Resolution of Z-(±)-Ethylmethyl-α-methoxy-β-styrylsulfonium Methyl Sulfate ((±)-13)

The difficulties encountered in the resolution of this salt are shown by the non-reproducability of the following three experiments.

Experiment one:

Racemic 13 (5.50 g, 17.2 mmole) was dissolved in a minimum amount of methanol and eluted through an hydroxide exchange column into a flask containing HDBT (6.46 g, 17.2 mmole). The solvent was concentrated to 75 ml. on a rotary evaporator, ether added to the cloud point and the mixture refrigerated at 5°. The precipitate was isolated to yield 6.6 g (11.0 mmole) ethylmethyl-2,2-dimethoxy-2-phenylethyl-sulfonium hydrogen 2(R),3(R)-dibenzoyltartrate (16): m.p. 129°; $[\alpha]_{589}^{RT}$ - 75.6° (c 0.452, methanol); N.M.R. (DMSO-d_6), δ 8.08 - 7.17 (m, 15H), 5.64 (s, 2H), 4.05 (s,2H), 3.26 (q, J = 7.0 cps, 2H), 3.20 (s, 6H), 2.73 (s, 3H), 1.22 (t, J - 7.0 cps, 3H); Infrared (nujol), 1728 (s), 1670 (m), 1600 (w), 1585 (w), 1260 (s), 710 (m) cm^{-1}.

Anal. Calcd. for $C_{31}H_{34}O_{10}S$: C, 62.20; H, 5.72; S, 5.36. Found: C, 62.51,,62.41; H, 5.74, 5.63; S, 5.35, 5.57.

Experiment two:

Racemic 13 (2.75 g, 8.58 mmole) was dissolved in a minimum amount of methanol and eluted through an hydroxide exchange column into HDBT (3.15 g, 8.48 mmole). The solution was concentrated to ca. 50 ml., ether added to the cloud point and the mixture cooled at 5°. The precipitate was isolated to yield 1.39 g (2.46 mmole) ethylmethyl-α-methoxy-β-styrylsulfonium hydrogen 2(R),3(R)-dibenzoyltartrate (17) m.p. 114°; $[\alpha]_{589}^{RT}$ - 78.2° (c 0.597, methanol); N.M.R. (DMSO-d_6), δ 8.00 - 7.10 (m, 15H), 6.26 (m, 3H), 6.08 (s, 1H), 5.70 (s, 2H),

3.76 (s, 3H), 3.43 (q, J = 7.0 cps, 2H), 3.03 (s, 3H), 1.30 (t, J = 7.0 cps, 3H); Infrared (nujol), 3500 (w), 1715 (s), 1645 (m), 1625 (m), 1600 (w), 1255 (s), 1110 (m), 715 (s) cm^{-1}.

Anal. Calcd. for $C_{30}H_{32}O_{10}S$: C, 61.63; H, 5.52; S, 5.48. Found: C, 61.75, 61.40; H, 5.51, 5.54; S, 5.54, 5.74.

Experiment three:

Racemic 13 (4.68 g, 14.6 mmole) was dissolved in a minimum amount of methanol and eluted through an hydroxide exchange column into HDBT (5.45 g, 14.5 mmole). The solvent was concentrated to ca. 30 ml., ether added to the cloud point and the mixture cooled at 5°. The precipitate was filtered to yield 2.67 g of a 3/2 mixture (by N.M.R.) of the vinyl/Michael-addition sulfonium DBT salts 17/16, m.p. 114 - 120°.

In each of the above three experiments a second crop of material was obtained by the addition of more ether and the cooling at 5° of the resulting mixture. After filtering the second crop, the mother liquor was concentrated to near dryness and excess ether added. After cooling the mixture at 5°, the supernatant was decanted leaving a tacky white semi-solid which solidified to a hard cake under reduced pressure. This material became the third crop. The first and third crops from these resolutions were then converted to their perchlorates.

Exchange of the first crop to perchlorate salts:

A 2.67 g quantity of a 3/2 mixture of vinyl/Michael-addition sulfonium DBT salt (first crop) was dissolved in methanol and eluted through an hydroxide exchange column into 0.72 g (5.04 mmole) 70% $HClO_4$. The solution was neutralized by the addition of dilute sodium methoxide,

reduced in volume, ether added to the cloud point and the mixture cooled at 5°. The precipitate was filtered to yield 0.361 g (1.17 mmole) (-)-ethylmethyl-α-methoxy-β-styrylsulfonium perchlorate ((-)-18); m.p. 115°; $[\alpha]^{RT}_{365}$ - 8.80° (c 0.716, methanol); N.M.R. (DMSO-d_6), δ 7.56 (s, 5H), 6.02 (s, 1H), 3.79 (s, 3H), 3.43 (q, J = 7.0 cps, 2H), 3.04 (s, 3H), 1.36 (t, J = 7.0 cps, 3H); Infrared ($CHCl_3$), 1610 (m), 1570 (w), 1490 (w), 1450 (m), 1080 (s), 1000 (m), 970 (w) cm^{-1}. Excess ether was added to the mother liquor to yield 0.621 g (1.82 mmole) (+)-ethylmethyl-2,2-dimethoxy-2-phenylethylsulfonium perchlorate ((+)-19); m.p. 65 ; $[\alpha]^{RT}_{365}$ + 4.75° (c 0.642, methanol); N.M.R. (DMSO-d_6), δ 7.55 (s, 5H), 4.03 (s, 2H), 3.24 (q, J = 7.0 cps, 2H), 3.28 (s, 6H), 2.72 (s, 3H), 1.73 (t, J = 7.0 cps, 3H); Infrared ($CHCl_3$), 2840 (w), 1490 (w), 1450 (m), 1420 (w), 1285 (m), 1090 (s), 703 (m), 622 (m) cm^{-1}. The conversion of a sample of pure Michael-addition sulfonium DBT salt (first crop) to its perchlorate gave an 85% yield of (+)-19 not contaminated by any of the vinyl salt.

Exchange of the third crop to perchlorate salts:

A 1.77 quantity of a 2/1 mixture of vinyl/Michael-addition sulfonium sulfonium DBT salt (third crop) was dissolved in methanol and eluted through an hydroxide exchange column into 0.491 g (3.45 mmole) 70% $HClO_4$. The solution was neutralized by the addition of dilute sodium methoxide, reduced in volume, ether added to the cloud point and the mixture cooled at 5°. The crystals were collected to yield 0.435 g (1.47 mmole) Z-(+)-18; m.p. 114°; $[\alpha]^{RT}_{365}$ + 8.84° (c 0.842, methanol). The N.M.R. and Infrared spectra were superimposible with those of the (-)-isomer. Ether was added to the mother liquor

to isolate impure (-)-19, m.p. 55 - 75°. In another experiment a third crop was processed as above to yield (-)-19: m.p. 55°; $[\alpha]^{RT}_{365}$ - 5.16° (c 1.14, methanol).

These perchlorates 18 and 19 did not give satisfactory carbon and hydrogen analysis because the samples exploded upon combustion analysis.

Benzyl p-Toluenesulfonate

Benzyl alcohol (10 ml., 97 mmole) was dissolved in 100 ml. anhydrous ether. Sodium hydride (4.2 g of 57% NaH, 100 mmole) was added and the solution stirred for 18 hours at room temperature. The suspension of sodium alcoholate was cooled in a wet-ice slurry and tosyl chloride (19.5 g, 97 mmole) in 100 ml. ether added dropwise. The mixture was stirred for 2 hours at 0° and one hour at room temperature. The reaction mixture was filtered and the mother liquor evaporated. The residual oil was crystallized from ether at - 70°. These crystals were twice recrystallized from benzene-Skellysolve B solvent mixture to yield 6.58 g (25.2 mmole, 26%) benzyl tosylate: m.p. 61 - 62° (reported m.p. 58.5 - 58.9° (28)); N.M.R. ($CDCl_3$), δ 7.52 (q, 4H), 7.06 (m, 5H), 3.84 (m, 2H), 2.37 (s, 3H); Infrared (nujol), 1600 (m), 1500 (m), 1350 (s), 1170 (s) cm^{-1}.

Alkylation of Ethylmethylsulfonium Phenacylid with Benzyl Tosylate

Benzyl tosylate (1.56 g, 5.98 mmole) and (±)-5 (1.12 g, 5.78 mmole) were dissolved in 25 ml. of THF. After stirring the mixture for 20 hours at room temperature, the solvent was removed. An N.M.R. seectrum of the residual oil showed the presence of the O-benzylated product as the major component. Attempted crystallization of the residual oil from a methanol-ether solvent mixture yielded another oil. The N.M.R. spectrum of this latter oil was similar to the crude material in most respects. The tosylate anion was exchanged for perchlorate by eluting a methanolic solution of the oil through an hydroxide exchange column and titrating the eluate with dilute perchloric acid. The neutralized eluate was concentrated, ether added to the cloud point and the mixture cooled at 5°. The precipitate was filtered to yield 0.551 g material: m.p. 111 - 113°; N.M.R. ($CDCl_3$), δ 7.6 - 7.2 (m, 10H), 5.81 (s, 1H), 4.98 (s, 2H), 3.26 (q, J = 7.0 cps, 2H), 2.73 (s, 3H), 1.23 (t, 3H), 5.32 (s, impurity), 2.98 (s, impurity); Infrared (nujol), 1680 (w), 1605 (s), 1080 (broad) cm^{-1}. The impurity resonances corresponded to those expected for a 16% yield of ethylmethylphenacylsulfonium perchlorate (15) in the salt. The vinyl salt appeared to be isomerically pure in configuration about the olefinic bond.

Polarimetric Rates

Method I:

The sample was accurately weighed into a 10 ml. tared volumetric flask. Solvent was added to the mark and the flask shaken until a homogeneous solution was obtained. An aliquot of the solution of the optically active sample was placed in a ca. 5 ml. thermostated polarimeter cell. The cell was maintained at 25.00 ± 0.02 and 50.0 ± 0.02° as required, by water circulating from a Colora Ultra-Thermostat bath. The first reading was taken after 5 minutes to ensure temperature equilibration. The optical rotation was taken from the digital readout of a Perkin-Elmer Polarimeter Model 141 at the appropriate time intervals. For the faster rates, time was recorded from a Lab-Cron 1400 timer. A "blank" reading was taken after each observation by recording the rotation of the cell chamber in the absence of the polarimeter cell. The rate constants were calculated on the basis of an experimental infinity obtained after 10 half-lives (zero rotation). After 10 half-lives of reaction at 50°, the racemized sample was concentrated to dryness and the residue submitted for N.M.R. analysis. As the spectra of the racemized materials were superimposible with those of synthetic racemic materials, within the experimental limits, there was no decomposition of the substrate.

Method II:

The sample was accurately weighed into a 50 ml. tared volumetric flask. Solvent was added to the mark and the flask shaked until a homogeneous solution was obtained. Aliquots of ca. 5 ml. were transfered to ampoules. The ampoules were sealed and placed in

constant temperature oil baths thermostated at 25.00 ± 0.03, 50.00 ± 0.03 and 70.00 ± 0.03° as required. At the appropriate time intervals, the ampoules were removed from the bath and immediately cooled in a wet-ice slurry. The first point was taken at least 5 minutes after the ampoules had been immersed in the bath so as to ensure temperature equilibration. The ampoules were opened and an aliquot transferred to a polarimeter cell at room temperature. The rotation was immediately recorded. All subsequent handling of the samples was similar to that described for Method I.

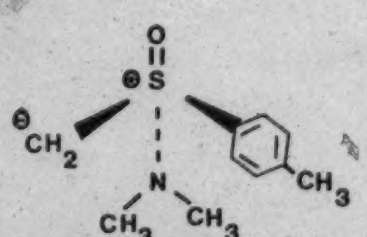
CHAPTER THREE

CHIRAL SULFONIUM YLIDS AS AGENTS OF ASYMMETRIC SYNTHESIS

Introduction

The general utility of the reaction of sulfonium ylids with aldehydes and ketones to yield the corresponding oxiranes has been reported by Corey and Chaykovsky (29), A. W. Johnson, Hruby and Williams (30) and Franzen and Driessen (31). The highly reactive sulfonium alkylids were typically generated at low temperatures *in situ* by the addition of suitable bases to solutions of the corresponding salts in inert solvents. Trost has found that the crystalline phenacylid 8 failed to react with cyclohexanone but did slowly condense in a Michael fashion with chalcone and dibenzoylethylene to yield cyclopropane products (32). The same ylid has also been reported to react in low yield with *p*-nitrobenzaldehyde (15). Numerous recent reports describe phenacylids and diacylmethylids as reactants with highly reactive electrophiles for the synthesis of several achiral heterocyclic systems (33).

C. R. Johnson and Schroeck (34) in 1968 reported the synthesis of optically active cyclopropanes and oxiranes using the optically active methylene transfer agent (*R*)-(-)-*N*,*N*-dimethylamino-*p*-tolyloxosulfonium methylid ((-)-20). In all cases where comparative data for other



(R)-(-)-20

asymmetric synthesis of the same active cyclopropanes and oxiranes were available, the optical purities obtained were the highest reported for direct asymmetric synthesis. Previously an asymmetric synthesis of 2-arylcyclopropyl carboxylic acids by the reaction of achiral dimethyloxosulfonium methylid with chiral β-arlyacrylates had been reported by Nozaki and co-workers (35). These examples of asymmetric synthesis with oxosulfonium ylids prompted this investigation of chiral sulfonium ylids as agents for asymmetric synthesis.

The reduced nucleophilicity anticipated for the chiral sulfonium ylids described in Chapter Two, and their facile racemization suggested that the selection of a more reactive ylid was necessary. Of the variety of optically active sulfonium salts characterized in these laboratories, ethylmethyl-p-nitrobenzylsulfonium perchlorate (21) (36) was chosen a suitable precursor of a reactive ylid. During a study of the racemization of substituted benzylsulfonium salts (36b), it was required to prepare the salt 21 from its corresponding methyl sulfate using an hydroxide exchange column. Upon elution of the methyl sulfate through the column, a deep wine-red colour formed which was ascribed to the formation of the corresponding ylid 22. Neutralization of the basic effluent with perchloric acid, with concomitant loss of the wine-red colour, yielded the perchlorate salt in 65% isolated yield. It was apparent that the sulfonium hydroxide and sulfonium ylid were in equilibrium in the methanolic solution. Furthermore, the exchange and equilibrium processes had little effect upon the chiral sulfonium center as optically active (+)-21 could be prepared by this sequence.

In 1961, Swain and Thornton (37) reported that dimethyl-p-nitrobenzylsulfonium p-toluenesulfonate (23), when treated with sodium hydroxide in water at 60°, was converted quantitatively to a mixture of Z and E-p,p'-dinitrostilbene. Based on their kinetic results and the product analysis, they postulated that the ylid 24 derived from 23 spontaneously decomposed to a carbene intermediate. Reinvestigations of this reaction by U. Schulz (38) and by Closs and Goh (39) showed that the ylid 24 decomposed to a much more complicated product mixture by means other that a carbene-sulfide decomposition route. A mechanism involving electron transfer from the ylid 24 to the sulfonium salt 23 was proposed to account for all the products. Several attempts by Schulz to isolate the ylid 24 failed however.

It seemed reasonable that the sulfonium ylid concentration in the coloured effluent might be sufficient to allow trapping reactions of 22 by aldehydes and ketones. Related reactions have been shown to occur between aldehydes and the ylid from benzyldimethylsulfonium chloride in heated aqueous hydroxide solutions to produce oxiranes in high yields (40,41). A. W. Johnson's technique for the generation of benzylids in aprotic solvents was considered a more laborious technique requiring more stringent experimental conditions than the proposed column technique used to prepare the wine-red equilibrium solution of the sulfonium hydroxide and ylid. Therefore, a study of the ability of chiral sulfonium ylids to transfer asymmetry from sulfur to carbon was initiated using (+)-21 as a suitable precursor of an optically active sulfonium ylid.

Synthesis and Resolution of Ethylmethyl-p-nitrobenzylsulfonium Perchlorate

Optically active ethylmethyl-p-nitrobenzylsulfonium perchlorate was prepared according to the procedure of Darwish and Hui (36) as illustrated in Figure XI. Ethyl p-nitrobenzyl sulfide was prepared by the treatment of α-bromo-p-nitrotoluene with sodium ethanethiolate in methanol. This sulfide was readily alkylated in acetone with dimethyl sulfate to yield (±)-ethylmethyl-p-nitrobenzylsulfonium methyl sulfate ((±)-25). The salt 25 was resolved by the fractional crystallization of its DBT salt prepared by the exchange techniques described in Chapter Two. The two diastereoisomers were easily separable as the less soluble isomer 26, m.p. 150°, $[\alpha]^{RT}_{589}$ - 71.5°, $[\alpha]^{RT}_{436}$ - 172° (c 0.27, methanol) (reported $[\alpha]^{25}_{589}$ - 68.8° (c 0.55, methanol) (36)) and the more soluble isomer 27, m.p. 141°, $[\alpha]^{RT}_{436}$ - 207° (c 0.25, methanol). The less soluble diastereoisomer was suspended

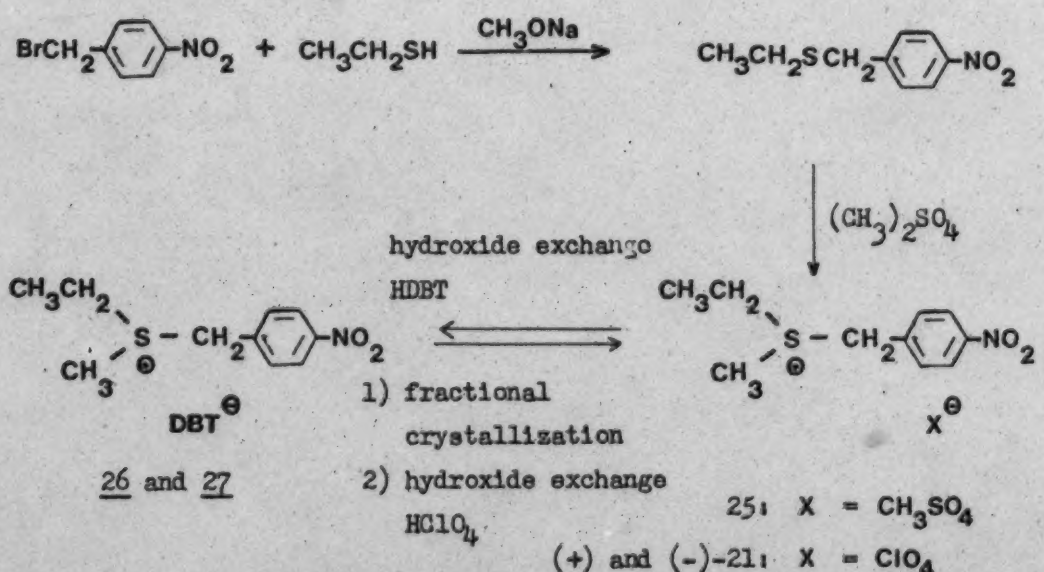


Figure XI. Synthesis and resolution of ethylmethyl-p-nitrobenzylsulfonium perchlorate.

on the top of an hydroxide exchange column and warm methanol was continuously eluted through the column until the effluent was no longer red in colour. As the effluent was collected, it was titrated with dilute perchloric acid using the ylid as an internal indicator. The neutralized effluent was concentrated to precipitate the salt (+)-21, m.p. 80°, $[\alpha]_{589}^{RT}$ + 17.9°, $[\alpha]_{436}^{RT}$ + 41.4° (c 0.459, methanol) (reported m.p. 83.5 - 85°, $[\alpha]_{589}^{RT}$ + 7.6° (c 0.9, methanol) (36)). The more soluble diastereoisomer was converted similarly to its perchlorate (-)-21, m.p. 80°, $[\alpha]_{589}^{RT}$ - 15.4°, $[\alpha]_{436}^{RT}$ - 37.7° (c 0.408, methanol).

Test Reactions for the Asymmetric Induction Experiments

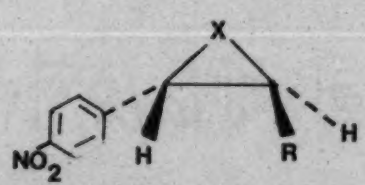
The nucleophilicity of the ylid 22 in the coloured effluent was tested by reaction with carbonyl compounds. Rather than titrating the effluent prepared by eluting ca. 1 g of 25 through an hydroxide exchange column with acid to generate a salt, various aldehydes, ketones and an α,β-unsaturated ketone were added and the solutions stirred at room temperature. The results of these experiments are summarized in Table VIII. A gradual loss of the wine-red colour was observed in all cases to yield eventually yellow-orange coloured solutions. However, the rate of loss of the initial colour was found to be dependent upon the electrophile added. After the colour had faded, the reaction mixtures were concentrated. The yellow evaporation residues obtained for the reactions with aldehydes were crystallized to give the oxiranes 28 to 31 in 65 - 77% yields. The oxiranes were assigned the trans configuration based on an analogy with A. W. Johnson's observation that trans-p-nitrostilbene oxide was formed exclusively in the reaction of dimethylsulfonium benzylid with p-nitrobenzaldehyde (30). Furthermore, the melting points for 28 and 30 agreed with the literature values available for oxiranes of the trans configuration (30, 42). The small N.M.R. coupling constants of ca. 1.6 cps for the methine protons were within the range of 1.4 - 3.1 cps expected for trans oxiranes versus the range of 2.2 - 4.5 cps for cis oxiranes (43).

In the reactions with ketones and chalcone, the colour of the reaction solution persisted for longer periods of time. The evaporation residue in each case was a red oil. Crystallization of each residue from benzene-Skellysolve B solvent mixture yielded small amounts of

TABLE VIII

TEST REACTIONS FOR THE ASYMMETRIC INDUCTION EXPERIMENTS

Added Reagent with 22	Reaction Time[a]	Product	M.p., °C	% Yield
benzaldehyde	1 hour	oxirane 28	124	65.5
p-chlorobenzaldehyde	1 "	" 29	125	77.3
p-nitrobenzaldehyde	1 "	" 30	200	77.3
acetaldehyde	½ "	" 31	86	66.0
chalcone	2 "	32	104	16.0[b,c]



trans-28: R = C_6H_5-, X = O

trans-29: R = p-ClC_6H_4-, X = O

trans-30: R = p-$NO_2C_6H_4$-, X = O

trans-31: R = CH_3-, X = O

32: R = C_6H_5CO-, X = C_6H_5CH-

p-nitroacetophenone	7 - 9 hours	no oxirane[b]
acetone	"	"
benzophenone	"	"
cyclohexanone	"	"

a: Time for the wine-red colour to disappear.

b: Sulfide decomposition products and oxirane 30 observed.

c: Stereochemistry not assigned.

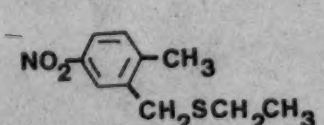
a high melting yellow material which was found to be identical with the oxirane 30 obtained in the reaction of the ylid 22 with p-nitrobenzaldehyde. In the reaction with chalcone, a second crop of material was isolated which corresponded to a 16% yield of a cyclopropane adduct. In all these latter cases, the mother liquors upon concentration to dryness exhibited similar N.M.R. spectra. No peaks could be assigned to products of oxirane formation. Rather, the major decomposition products were considered to be sulfides from the Sommelet rearrangement because of the resonance pattern in the high field region of the spectra.

Schultz, in his reinvestigation of the reaction of 23 with aqueous sodium hydroxide solution at 100°, found a total of eight compounds of combined yield of ca. 50%: p,p'-dinitro derivatives of stilbene, tolane, bibenzyl and stilbene oxide and p-nitro derivatives of benzyl alcohol, benzaldehyde, benzoic acid and toluene. The remaining material was considered to be polymeric in nature. In addition, Schulz detected an almost quantitative loss of dimethyl sulfide. The isolation of trans-30 in the reactions with added ketones and chalcone suggested that the ylid 22 was decomposing in a manner similar to that proposed by Schulz. However, the presence of non-volatile sulfides in the product was a significant departure from the quantitative loss of dimethyl sulfide in the decomposition of 23. Therefore, a major effort was initiated to confirm the identity of the sulfur containing materials of the evaporation residues.

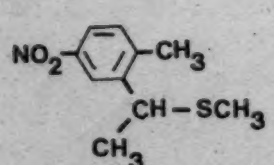
The Sommelet (44) and Stevens (45) rearrangements of sulfonium salts are well known. Yoshimine and Hatch (40) reported trace amounts of sulfides originating from either a Sommelet or Stevens rearrangement during an oxirane synthesis using benzyldimethylsulfonium

chloride in aqueous hydroxide solution. Hayashi and Oda (46) studied the methoxide catalyzed rearrangement of various p-substituted benzyl sulfonium salts and report high yields of the corresponding Sommelet rearrangement products. However, the p-nitrobenzyl system was not studied because of an anticipated quantitative decomposition of the salt to dinitrostilbene as reported by Swain and Thornton.

The N.M.R. spectra of the residues from reaction of 22 with ketones showed the following major signals neglecting those contributed by the ketones: δ 1.25 (t), 1.58 (d), 1.95 (s), 2.48 (s), 2.51 (q) and 4.16 (q). In addition to these signals, there were other singlets in the region δ 8.00 - 4.50 of much smaller intensity. Furthermore, the aromatic region was not indicative of a simple para-substituted nitro-aromatic compound(s). The coupling constants and the chemical shifts suggested the presence of an ethyl group and an α-arylethyl substituted group. The Sommelet sulfides expected from the rearrangement of 25 were ethyl 2-methyl-5-nitrobenzyl sulfide (33) and methyl α-(2-methyl-5-nitrophenyl)ethyl sulfide (34). The major resonances of the N.M.R. spectra of the evaporation residues supported these structures. The relative ratios of the two sulfides 34/33 was ca. 2/1 as gauged by the relative intensities of the doublet and triplet in the spectra.



33



34

The sulfide 34 was isolated in pure form from the residue of the reaction of 22 with acetone by column chromatography. The sulfide 33 could not be isolated pure as it was contaminated with small amounts of the faster eluting 34. These sulfides were partially separated by gas-liquid chromatography however their overlap prevented a quantitative analysis or isolation at the collection port of the GLC. A literature survey proved these sulfides to be unknown. Therefore, their assignments were confirmed by comparison with authentic samples prepared by independent methods.

Although the pyramidal configuration of (±)-21 has been confirmed by X-ray crystallography (46), a correlation between the sign of rotation of an active isomer and absolute configuration of the salt has not been made. Therefore, it would have been impossible to make a configurational assignment of the potentially optically active 34 from the Sommelet rearrangement based on a mechanistic scheme for the rearrangement of the salt (+)-21. For this reason, a literature procedure for the Sommelet rearrangement (47) was considered for p-chlorobenzylethylmethylsulfonium perchlorate (±)-35 (48), the (+)-isomer of which has been assigned the R configuration from X-ray crystallography studies (46).

p-Chlorobenzylethylmethylsulfonium perchlorate was prepared as follows. p-Chlorobenzaldehyde was reduced to the corresponding alcohol 36 with sodium borohydride. The bromide 37 was obtained by bubbling hydrogen bromide gas through a benzene solution of 36. (±)-p-Chlorobenzylethylmethylsulfonium bromide (38) was obtained by

the nucleophilic displacement of ethyl methyl sulfide on 37 in acetone. The unstable bromide salt was converted to its perchlorate (±)-35 by the exchange techniques described earlier. The salt was resolved by the fractional crystallization of its DBT salt. Regeneration of the perchlorate from the less soluble diastereoisomer 39, $[\alpha]^{RT}_{589}$ - 71.8°, $[\alpha]^{RT}_{436}$ - 174° (c 1.52, methanol) (reported $[\alpha]^{RT}_{589}$ - 69.6° (c 1.6, methanol (48)), yielded (R)-(+)-35, $[\alpha]^{RT}_{365}$ + 62.2° (c 0.60, methanol) (reported $[\alpha]^{RT}_{365}$ + 56.2° (48)). The more soluble diastereoisomer 40 $[\alpha]^{RT}_{436}$ - 198° (c 1.39, methanol) gave (S)-(-)-35, $[\alpha]^{RT}_{365}$ - 43.5° (c 1.8, methanol).

The salt (±)-35 was decomposed at 70° in two hours in the presence of 10 equivalents of a 24% sodium methoxide solution. The presence of three compounds in the product was indicated by N.M.R. spectroscopy: methyl α-(2-methyl-5-chlorophenyl)ethyl sulfide (41), ethyl 2-methyl-5-chlorobenzyl sulfide (42) and methyl p-chlorobenzyl ether (43) in the relative yields of 4:1:1 respectively. In this case the decomposition products were sufficiently separated by GLC to permit quantitative analysis and recovery of the components at the collection port. Their assignments were confirmed by comparison of their spectra with those for authentic samples prepared by independent methods.

Preparation of the Sommelet Sulfides

The reaction sequences for the preparation of the Sommelet sulfides are summarized in Figures XII and XIII.

Ethyl 2-methyl-5-nitrobenzyl sulfide (33) was prepared by the nucleophilic displacement of sodium ethanethiolate on 2-chloromethyl-4-nitrotoluene (44) (49) in methanol. The chloride 44 had been prepared by the chloromethylation of p-nitrotoluene with bis-chloromethyl ether (50) and chlorosulfonic acid. The chloride had to be handled carefully as it was a lacrymator and a skin irritant. The liquid sulfide 33 was oxidized by excess H_2O_2 in acetic acid to provide the solid sulfone derivative 45.

The sulfide 34 was prepared in a 7-step sequence from 2-methyl-5-nitroaniline. 2-Cyano-4-nitrotoluene (46) was prepared by a Sandmeyer reaction of cuprous cyanide and the diazotized amine. The nitrile was hydrolyzed according to a literature method (52) for an analagous substrate in aqueous hot sulfuric acid solution to yield 2-methyl-5-nitrobenzoic acid (47) (53). When the solid acid was slowly added to thionyl chloride at 60° over a period of 3 hours and the excess solvent removed under reduced pressure, 2-methyl-5-nitrobenzoyl chloride (48) (54) could be obtained only slightly contaminated by the high melting 2-methyl-5-nitrobenzoic anhydride (49). The anhydride was easily removed by fractional crystallization from benzene-Skellysolve B solvent mixture. If thionyl chloride was refluxed during the addition, greater amounts of 49 resulted. 2-Methyl-5-nitroacetophenone (50) was prepared in a low 25% yield in a departure from the published procedure (55) by reaction of a crude acid chloride sample, containing 49, with dimethyl cadmium in

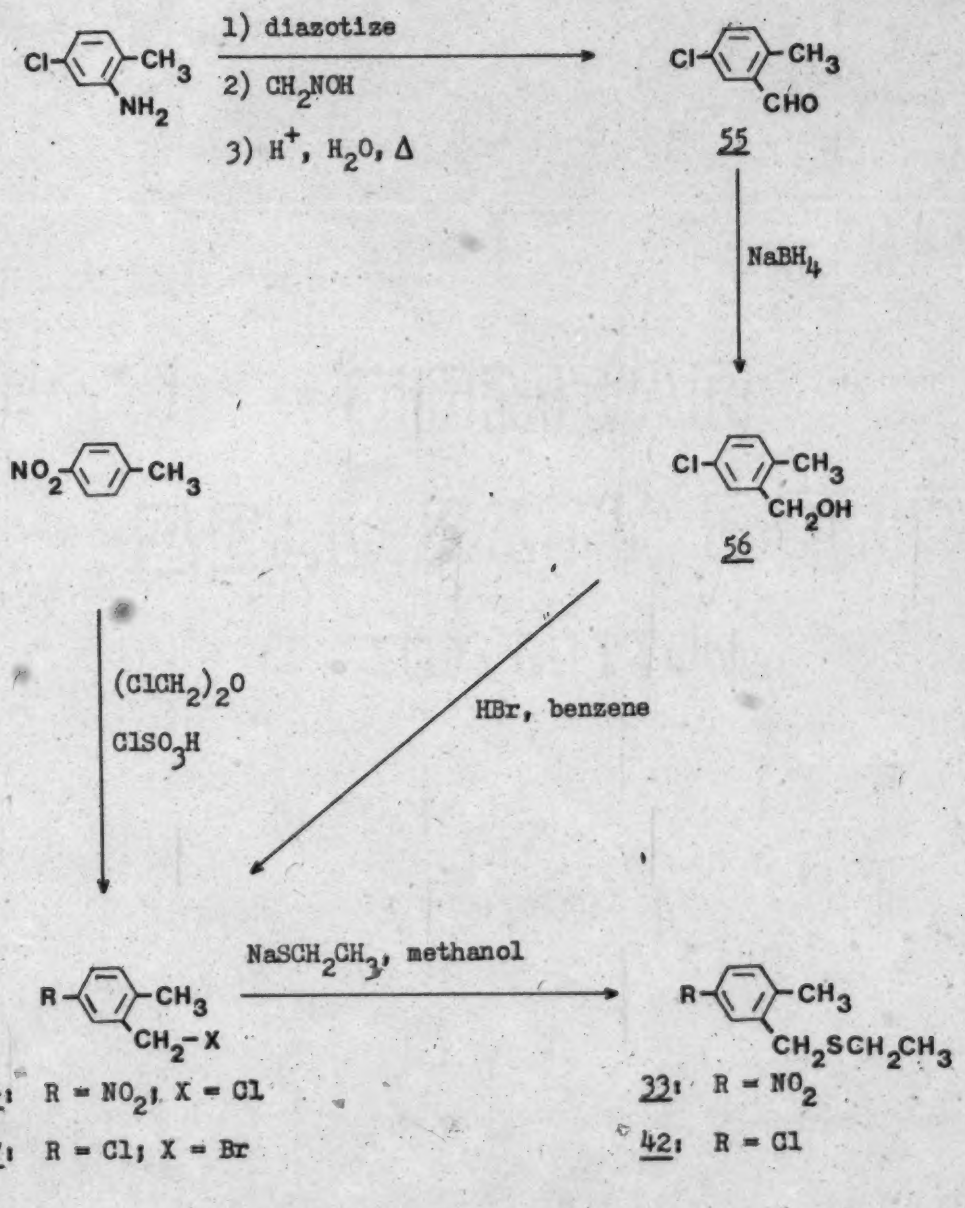


Figure XII. Preparation of the ethyl-Sommelet sulfides 33 and 42.

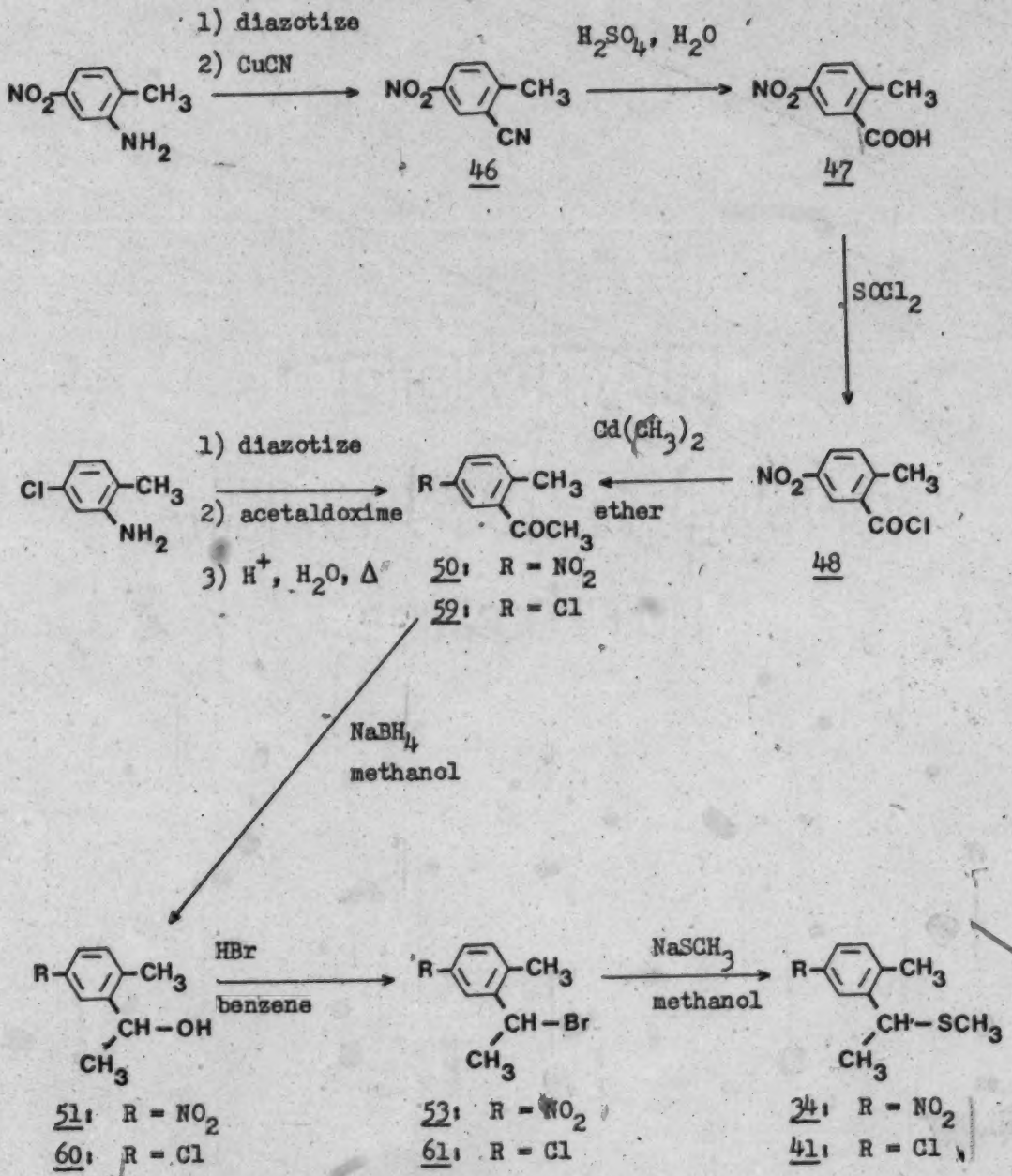


Figure XIII. Preparation of the methyl-Sommelet sulfides 34 and 41.

ether solvent at reflux for 75 minutes. Aromatic nitroanhydrides (56) and acid chlorides (57) have been reported to react with organocadmium reagents to yield ketones. A purification step of the crude acid chloride was considered, therefore, not necessary. In some experiments small amounts of acid chloride were also co-distilled with the ketone. The ketone was reduced with sodium borohydride in methanol to yield α-(2-methyl-5-nitrophenyl)ethyl alcohol 51. Any acid chloride present during the reduction was solvolyzed to the corresponding ester 52 which remained in the mother liquor during the fractional crystallization of the crude 51. The alcohol was converted to the corresponding bromide 53 by bubbling HBr gas through a benzene solution of 51. Finally, 53 was treated with sodium methanethiolate in methanol to yield the sulfide 34, mp 49.5 - 50°. The sulfide was oxidized to its higher melting sulfone derivative 54 by excess H_2O_2 in acetic acid at 100°.

Ethyl 2-methyl-5-chlorobenzyl sulfide (42) was prepared as follows. 2-Methyl-5-chlorobenzaldehyde (55) (58) prepared by the method of Beech (59) in the reaction of formaldoxime with the diazotized 2-methyl-5-chloroaniline, was reduced to the alcohol 56 by sodium borohydride in methanol. The corresponding bromide 57 was prepared by bubbling HBr gas through a benzene solution of 56. Nucleophilic displacement of sodium ethanethiolate on 57 gave the liquid sulfide 42. Oxidation of the sulfide by excess H_2O_2 in acetic acid gave the corresponding solid sulfone 58.

The second chloro-Sommelet sulfide 41 was prepared from 2-methyl-5-chloroacetophenone 59 (60) obtained in a procedure similar

to that for the aldehyde 55 by the reaction of acetaldoxime (61) with diazotized 2-methyl-5-chloroaniline. The ketone 59 was reduced to the alcohol 60 by sodium borohydride reduction. The corresponding bromide 61 was obtained by bubbling HBr gas through a benzene solution of 60. Nucleophilic displacement of sodium ethanethiolate on 61 gave the liquid sulfide 41. Oxidation of 41 with excess H_2O_2 in acetic acid produced the solid sulfone 62.

p-Chlorobenzyl methyl ether, the product of displacement in the methoxide-catalyzed rearrangement was prepared from p-chlorobenzyl bromide (37) and sodium methoxide in methanol.

Asymmetric Induction Reactions

The ability of chiral sulfonium ylids to transfer asymmetry from sulfur to carbon was investigated in reactions identical to those just described for the racemic materials.

When optically active p-nitrobenzylid 22 prepared from (-)-21 was treated at room temperature with an equivalent of benzaldehyde, an optically active evaporation residue was obtained, $[\alpha]_{546}^{RT}$ + 6.37° (c 1.24, CH_2Cl_2). Crystallization of this material gave racemic oxirane 28 in 57% yield. The mother liquor after concentration gave a residue, $[\alpha]_{546}^{RT}$ + 12.1° (c 3.02, CH_2Cl_2) which could be crystallized to give active oxirane 28, $[\alpha]_{546}^{RT}$ + 5.51° (c 0.506, benzene). Again, however, the major activity resided with the material in the mother liquor which was shown by N.M.R. spectroscopy to consist of the desired oxirane plus some decomposition products including sulfide 34. A final 9 mg of solid material, $[\alpha]_{546}^{RT}$ + 20° (c 0.18, benzene), was obtained from this latter material.

The fact that the sign of rotation had changed after reaction was initially encouraging, however, significantly larger rotations would have been more useful in the analysis of the reaction products. From the fractional crystallization of the evaporation residue, it was not possible to assign the activity observed to the oxirane with confidence. Although the N.M.R. spectrum of the active oxirane 28 was superimposible upon that of racemic material, trace amounts of an active impurity could easily have escaped detection. The specific rotations calculated were subject to large experimental errors due to the small sample sizes and small observed rotations. The significant rotations remained in the mother liquors of each crystallization

suggesting that an optical fractionation of the racemic from the active oxirane was occurring. However, the presence of decomposition products in the active residues made the assignment of activity difficult.

When optically active ylid from (+)-21 was treated at room temperature with a large excess of acetaldehyde, the colour of the reaction solution faded almost immediately. After concentration of the reaction mixture, the residue was crystallized from benzene-Skellysolve B solvent mixture to yield the racemic oxirane 31 in 50% yield. When the evaporation residue of the mother liquor of this crystallization was triturated in hot Skellysolve B and the supernatant decanted from a red residual oil and cooled, active oxirane 31, $[\alpha]_{436}^{RT}$ - 4.9° (c 0.77, benzene) was isolated in 20% yield. The red residue, optically active, contained some oxirane as well as some decomposition products.

These experiments confirmed that asymmetric products were being produced, however, the origin of the activity remained in doubt. Even for the very fast reaction with excess acetaldehyde, considerable decomposition occurred possibly giving asymmetric products. Some of this decomposition may have occurred during the anion exchange reaction. The only compound readily identified from the N.M.R. spectrum of the the decomposition products was the Sommelet sulfide 34. There was the possibility that the activity originated with this sulfide.

To test this hypothesis, the changes in optical activity of a solution of the ylid derived from (+)-21 were followed at 25° and 50°. The results presented in the experimental section indicate a complex rate of change of optical activity with the reaction occurring in at least two stages. At 28,500 seconds reaction at 25°, the colour of

the ylid had faded and the solution had an observed rotation of 0.062°. Assuming that this indicated complete decomposition of the ylid, asymmetrical products had been formed. Some of the products were, however, optically labile as optical stability was not achieved until 10^5 seconds with an observed rotation of 0.028°. In another experiment, an aliquot of a decomposition solution of (±)-21, $[\alpha]_{436}^{RT}$ + 34.7° (c 1.06, methanol), was withdrawn after 9 hours reaction at room temperature and concentrated. Using benzhydrol as an internal standard, the yield of the two Sommelet sulfides 34 and 33 were estimated by N.M.R. spectroscopy to be 30 and 12% respectively. It was confirmed that the sulfide 34 contributed to the activity of the solution by isolation of the pure sulfide from the remaining solution by column chromatography. Pure non-crystallized 34, $[\alpha]_{589}^{RT}$ +, 19.7°, $[\alpha]_{578}^{RT}$ + 20.1°, $[\alpha]_{436}^{RT}$ + 42.7° (c 0.483, CH_2Cl_2), recrystallized from Skellysolve B, $[\alpha]_{436}^{RT}$ + 39.1° (c =.358, CH_2Cl_2) was obtained as the faster-eluting sulfide. Sulfide 33 could not be obtained pure, free of sulfide 34. If the decomposition of (+)-21, $[\alpha]_{436}^{RT}$ + 40.3° (c 0.94, methanol), was continued for 17 hours rather than 9 hours, the non-recrystallized sulfide 34 isolated had a specific rotation of $[\alpha]_{436}^{RT}$ + 54.2° (c = 0.512, CH_2Cl_2). Correcting for the differing optical purities of the starting sulfonium salts, the two reactions proceeded with almost identical degrees of asymmetric inductions in the sulfide 34. The changes of rotation after the loss of the ylid colour were therefore likely related to racemization of other unidentified products and not to the sulfide 34.

This isolation of the optically active sulfide 34 in June of 1971 was the first example of an asymmetric systhesis using a chiral

sulfonium ylid. Recently, Trost and Hammen (62) communicated their observation of an asymmetric synthesis in the [3,2] sigmatropic rearrangement of (+)-adamantylallylethylsulfonium tetrafluoroborate ((+)-63) to (R)-(-)-1-adamantyl-2-pent-4-enyl sulfide ((R)-64) under reversible ylid generation conditions with a minimum of 94% optical induction.

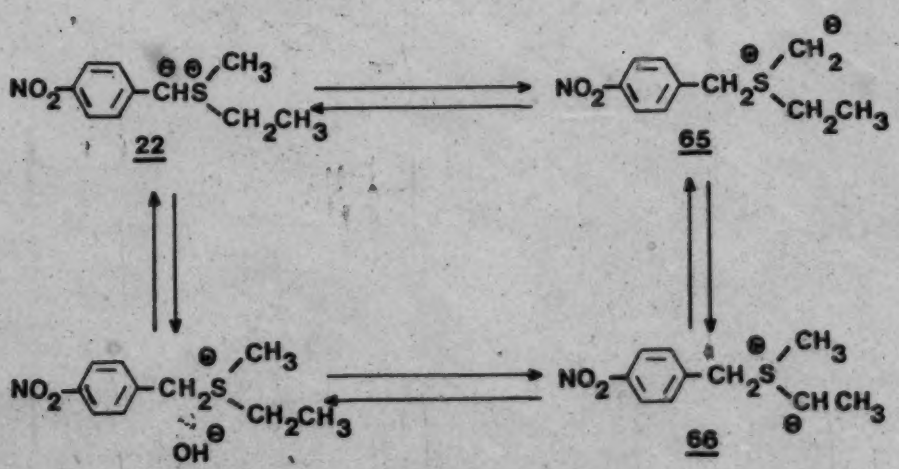
The observation of asymmetric induction in the sulfide product from the Sommelet rearrangement was extended to the literature procedure described earlier for substituted benzyldimethylsulfonium salts. When (R)-(+)-35, $[\alpha]^{RT}_{365}$ + 62.2° (c 0.598, methanol) was treated with methoxide ion in a manner described for the racemic material, the oil obtained after workup upon solution in 5 ml. benzene had an observed rotation of + 2.44°. Analysis by GLC using 2-methylnaphthalene as an internal standard showed the solution to contain compounds 41, 42 and 43 in 57.4, 13.4 and 29.3% yields respectively (corrected for 94% product balance). Based on the 57.4% yield of 41, the active sulfide had a specific rotation of $[\alpha]^{RT}_{436}$ + 67.4° (c 3.62, benzene).

The active sulfide (+)-41 was condensed in a U-tube at the collection port of the GLC instrument on successive injections of a concentrated solution of the oil. The condensed sample, $[\alpha]^{RT}_{436}$ + 66.2° (c 0.660, benzene) had spectral properties identical with those of the racemic material excepting optical rotation. Racemization during the chromatographic separation was ruled out by the identity of the specific rotations as determined before and after chromatography.

Discussion

The direct reaction of the ylid 22 generated in situ by the exchange techniques had many advantages of convenience and economy over reactions involving strong bases in inert solvents. The usual method of generating a reactive ylid required careful drying of the inert solvent and low temperature reactions. Furthermore, the extremely basic reagents used required careful handling techniques. The exchange techniques in this instance required none of these precautions.

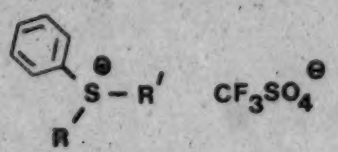
The condensation reactions with aldehydes gave oxiranes derived from ylid formation at the benzylid position. The acidifying effect of the p-nitrophenyl substituent resulted in the benzylid formed from the sulfonium hydroxide having sufficient concentration to permit facile condensation with aldehydes. That the benzylid 22 and its sulfonium hydroxide were also in equilibrium with the ylids 65 and 66 formed at the methyl and ethyl substituents, was evidenced by the isolation of the Sommelet sulfides in the absence of reactive electrophiles. The high yield of trans-28 from reaction with benzaldehyde, indicated



that the stabilized benzylid had a higher concentration than the more reactive ylids 65 and 66. As the reactions with the benzylid were slowed down, the reactions of the methylid and ethylid became more important resulting in products of the Sommelet rearrangement.

The optical yields in the asymmetric induction reactions with aldehydes were disappointingly low. Whereas the sign of rotation in the Sommelet rearrangement did not change in proceeding from salt to products, a sign inversion did occur in the reactions of 22 with aldehydes. If the rotation of the residues originated from active oxiranes, the predominance of racemic oxirane isolated and the small rotations of samples presumed to be pure oxirane, suggested that the extent of asymmetric induction was negligible. Although the absolute rotation of trans-28 is not available, a very large value for $[\alpha]^{RT}_{546}$ is anticipated on the basis of the known absolute rotation of trans-stilbene oxide (trans-2,3-diphenyloxirane) being $[A]^{RT}_{589}$ 310° (63) although the p-nitro substituent would alter the optical rotary power somewhat.

Darwish and Nakamura (64) have also observed low optical yields in the oxirane synthesis from chiral sulfonium ylids with aldehydes. For the ylids derived from the optically active sulfonium salts 67 by generation with lithium alkyls in dry THF at - 78° , essentially zero rotation of the oxirane product was observed in each reaction with benzaldehyde. Trost and Hammen (62) examined the ability of the



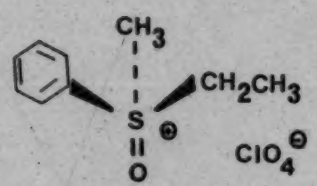
67a: R = p-anisyl, R' = CH_3
b: R = CH_2CH_3, R' = CH_3
c: R = p-anisyl, R' = CH_2CH_3

methylid from (+)-adamantylethylmethylsulfonium tetrafluoroborate (68) to produce active oxiranes in reaction with benzaldehyde. They also failed to observe significant rotations in the products.

These low optical yields for sulfonium ylids are in contrast with the significant yields obtained by C. R. Johnson and Schroeck for the oxosulfonium methylid (R)-(-)-20 (34). Johnson found the oxosulfonium methylid 20 to be similar in stability and reactivity with dimethyloxosulfonium methylid (69) rather than dimethylsulfonium methylid (70). These latter two ylids, as characterized by Corey and Chaykovsky, have different reactivities. For example, the simple ylid 70 underwent 1,2-carbonyl addition with α,β-unsaturated ketones to form oxiranes whereas the ylid 69 gave a cyclopropane adduct. C. R. Johnson and Schroeck have also found that the attack of stabilized ylids with aldehydes is reversible whereas the attack of a non-stabilized ylid such as 70 is irreversible (66). Trost has suggested that the differences in optical yields may be attributed to the higher reactivity of the non-stabilized sulfonium methylids.

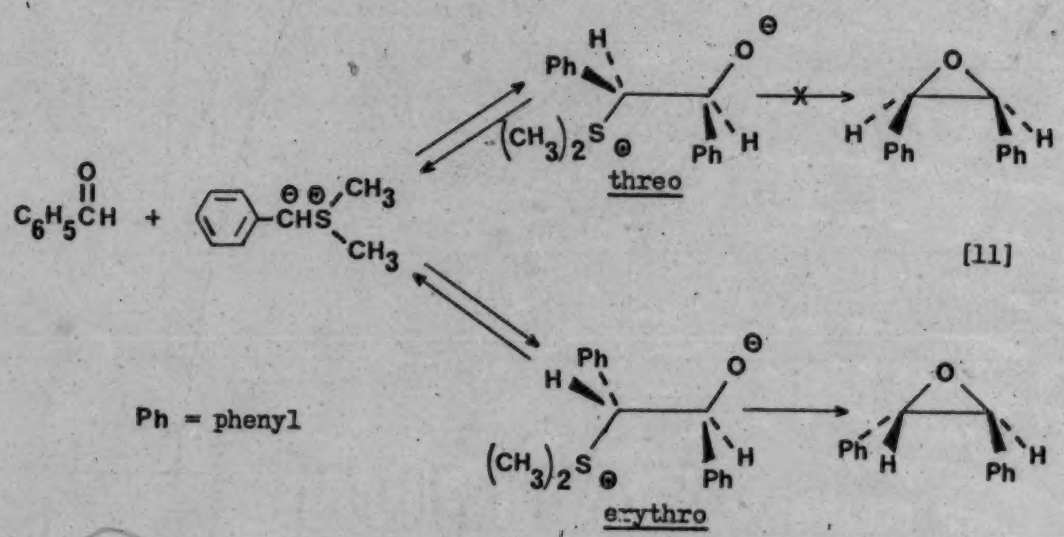
The ability to transfer asymmetry may depend upon the additional steric and electronic requirements of the oxygen ligand in an oxosulfonium ylid. The non-bonded interactions in the transition state involving this substituent may be more significant than the non-bonded interactions involving the lone pair of electrons on the sulfur. A comparison of the ability of the two classes of ylids to transfer asymmetry could be made by treating the ylid generated from (R)-(+)-ethylmethylphenyloxosulfonium perchlorate ((R)-(+)-71) recently described by Kobayashi and Minato (65), with aldehydes. The ylid would be

the oxygenated analogue of the ylid generated from the salt 67b described by Darwish and Nakamura. In addition, whatever influence the dimethylamino substituent had upon the course of the oxirane synthesis from 20 would be removed in using the ylid generated from (R)-(+)-71.



(R)-(+)-71

From the existing evidence, a chiral sulfonium methylid is incapable of inducing asymmetry at a developing tetrahedral center by a preferential attack of the methylid on one of the stereoheterotopic faces of an aldehyde function. An alternate method of transferring asymmetry to the oxirane product should be considered for sulfonium ylids generated at a pro-chiral center. Two new chiral centers are formed when a benzylid condenses with an aldehyde, one each from the benzylid and aldehyde carbons. However, the geometry of the carbon originating from the aldehyde is dictated by the configuration of the attacking benzylid as exclusively trans geometry is observed in the oxirane product. A. W. Johnson has proposed the mechanistic scheme illustrated by eq. [11] for the reaction of a benzylid with benzaldehyde. Of the two betaine conformations required for internal S_N2 ring closure to the oxirane, the threo conformer has three bulky groups gauche to each other thus raising the energy of this conformer. The transition state for ring closure from the threo form would be higher in energy than that from the erythro form because of the eclipsing of the phenyl rings.



[11]

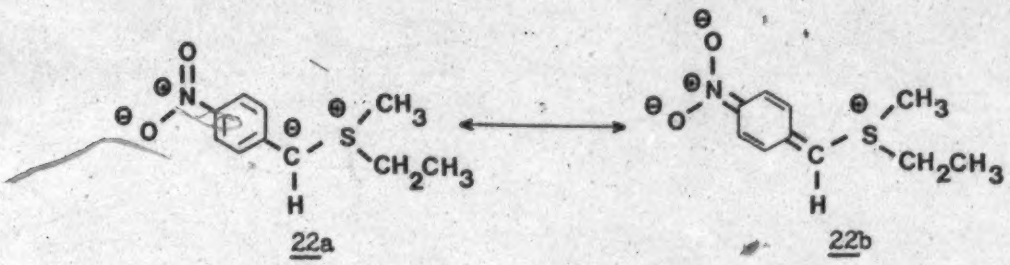
Therefore the stereochemistry of the asymmetric center originating with the aldehyde is determined by the stereochemistry of the attacking carbon nucleophile and not by the β-sulfonium center. If the stereochemistry of the nucleophilic center is affected by the adjacent chiral sulfonium center, then an asymmetric synthesis of the oxirane would result.

Wolfe recently summarized his theoretical and experimental studies on the Gauche Effect (67). The Gauche Effect describes the tendency of a species to adopt a structure which has the maximum number of gauche interactions between adjacent electron pairs and/or polar bonds. Carrying out ab initio molecular orbital calculations on models such an H_2O_2, N_2H_2, FCH_2OH and others, the energy profile as a function of rotation led Wolfe to conclude that the most stable structure contained the maximum number of gauche interactions. By applying these

theories of the Gauche Effect to sulfonium salt and ylid chemistry, Wolfe postulated a selective removal of that methylene proton gauche to the electron pair on sulfur with induction of asymmetry at the α-carbon.

Experimentally Wolfe found there to be a diastereotopic selectivity of the benzylic protons in the base-catalyzed deuterium exchange of benzyl methyl sulfoxide (72) to give predominately the RS(SR) diastereomer (68). However others subsequently found the exchange rate of 72 to be solvent dependent such that the SS(RR) diastereomer could be obtained almost exclusively (69). Furthermore, R. R. Fraser and coworkers studied the H/D exchange of the diastereomeric hydrogens in a conformationally rigid sulfoxide and found a solvent dependence upon the relative rates of exchange (70). The inability of the theory to predict carbanion stability was attributed to the inability of the MO calculations to include the effects of solvation.

The low optical yields in the oxirane synthesis from the p-nitrobenzylid 22 suggested that there was little selectivity between the diastereotopic benzylic hydrogens during ylid formation assuming the configuration of the α-carbanion was preserved after ylid formation. That the configuration of the carbanion may have been lost is not unexpected in view of the low barriers to pyramidal inversion for tri-coordinated first-row atoms (25,71) and the expected delocalization of the carbanion into the nitro-aromatic ring (22b) thereby lowering the barrier even further. If the carbanionic center became racemized,



22a 22b

the chiral sulfonium group apparently did not induce a greater nucleophilicity at either the re or si face of the average planar configuration of the carbanion. Racemization of the ylid at the sulfur center could not account for the low asymmetric induction as the reactions with aldehydes proceeded more rapidly than the Sommelet rearrangement, for which active products were isolated.

Before rationalizing the observation of asymmetric induction in the products of the Sommelet rearrangement, the experiments to determine the per cent asymmetric synthesis in the Sommelet sulfides will be described. These experiments are presented in Chapter Four.

Experimental

p-Nitrobenzyl Ethyl Sulfide

p-Nitrobenzyl ethyl sulfide was prepared in a manner similar to that described by Hellmann and Eberle (72). To a sodium methoxide solution prepared by dissolving 5.4 g (0.234 mole) clean sodium metal in 60 ml. methanol, was added 120 ml. ethyl mercaptan. With stirring, a 50 g quantity (0.232 mole) of α-bromo-p-nitrotoluene was added to the thiolate solution. After one hour, the reaction mixture was diluted with 100 ml. water and extracted several times with ether. The ether extracts were dried over magnesium sulfate and the solvent removed. The residue was distilled under reduced pressure to yield 42 g (0.213 mole, 92.2%) p-nitrobenzyl ethyl sulfide: b.p. 154 - 157° (4 mm), 170° (10 mm); N.M.R. ($CDCl_3$), δ 8.14 (d, J = 8.5 cps, 2H), 7.43 (d, J = 8.5 cps, 2H), 3.80 (s, 2H), 2.46 (q, J = 7.5 cps, 2H), 1.24 (t, J = 7.5 cps, 3H); Infrared (neat), 1600 (s), 1520 (s), 1345 (s), 1110 (m) cm^{-1}.

(±)-Ethylmethyl-p-nitrobenzylsulfonium Methylsulfate ((±)-25)

A quantity of 42 g (0.214 mole) p-nitrobenzyl ethyl sulfide was stirred with 28 g (0.222 mole) dimethyl sulfate in 50 ml. acetone overnight. The solvent was removed and the residue crystallized from methanol-ether solvent mixture to yield 59 g (0.183 mole, 85.5%) (±)-25: m.p. 102° (reported 93 - 95° (36b)); N.M.R. (DMSO-d_6), δ 8.42 (d, J = 9.0 cps, 2H), 7.89 (d, 9.0 cps, 2H), 4.96 (s, 2H), 3.52 (s, 3H), 3.44 (q, J = 7.5 cps, 2H), 2.95 (s, 3H), 1.40 (t, J = 7.5 cps, 3H); Infrared (nujol), 1610 (m), 1520 (s), 1460 (s), 1230 (s) cm^{-1}.

(-)-Ethylmethyl-p-nitrobenzylsulfonium Hydrogen 2(R),3(R)-Dibenzoyltartrate

A 13.1 g quantity (0.0406 mole) 25 was dissolved in a minimum amount of methanol and passed through an hydroxide exchange column into 15.2 g (0.0406 mole) HDBT. A wine-red colour, ascribed to the formation of the corresponding ylid generated on the exchange column, was immediately extinguished upon reaction with the acid. After the ylid was completely washed from the column, the resulting mixture was concentrated to 100 ml. and filtered to yield 8.35 g of the less soluble isomer 26; m.p. 150°; $[\alpha]_{589}^{RT}$ - 71.5°, $[\alpha]_{436}^{RT}$ - 172° (c 0.27, methanol) (reported $[\alpha]_{589}^{RT}$ - 68.8° (c 0.55, methanol) (36)); N.M.R. (DSMO-d_6), δ 8.5 - 7,4 (m, 14H), 5.70 (s, 2H), 4.89 (s, 2H), 3.35 (q, H = 7.5 cps, 2H), 2.83 (s, 3H), 1.29 (t, J = 7.5 cps, 3H); Infrared (nujol), 1710 (s), 1665 (m), 1525 (s), 1115 (m) cm^{-1}.

Anal. Calcd. for $C_{28}H_{27}NO_{10}S$: C, 59.04; H, 4.78; N, 2.46; S, 5.63. Found: C, 58.93, 58.91; H, 4.51, 4.88; N, 2.76, 2.65; S, 5.96, 5.87.

After cooling the mother liquor at 5°, a further 4.3 g material precipitated. Ether was added in excess to the mother liquor of this precipitate to precipitate after cooling at - 10°, the more soluble isomer 27; m.p. 141°; $[\alpha]_{436}^{RT}$ - 207° (c 0.25, methanol). The second crop of crystals was recrystallized from methanol-ether solvent mixture to yield 1.73 g of 26 and from the mother liquor, 2.16 g of 27. The overall yield of 26 and 27 was 19.4 g (0.0341 mole, 83.8%).

(+)-Ethylmethyl-p-nitrobenzylsulfonium Perchlorate ((+)-21)

A quantity of 9.8 g (17.2 mmole) 26 in 250 ml. methanol was applied to an hydroxide exchange column. Methanol (ca. 1500 ml.) was continuously washed through the column until the highly insoluble salt had dissolved and exchanged. The effluent was titrated with dilute methanolic $HClO_4$ using the ylid as an internal indicator. The solution was concentrated to 100 ml. while maintaining a bath temperature below 25°. Ether, added to the cold solution, precipitated 4.79 g (15.3 mmole, 89.2%) (+)-21: m.p. 80°; $[\alpha]^{RT}_{589}$ + 17.9°, $[\alpha]^{RT}_{436}$ + 41.4° (c 0.459, methanol) (reported $[\alpha]^{RT}_{589}$ + 7.6° (c 0.9, methanol); m.p. 83.5 - 85° (36)); N.M.R. (DMSO-d_6), δ 8.25 (d, J = 8.0 cps, 2H), 7.72 (d, J = 8.0 cps, 2H), 4.80 (s, 2H), 3.33 (q, J = 7.5 cps, 2H), 2.84 (s, 3H), 1.36 (t, J = 7.5 cps, 3H); Infrared (nujol), 1610 (s), 1500 (s), 1430 (s), 1100 (broad) cm^{-1}. The specific rotation reported is the highest obtained for several preparations of this salt.

Anal. Calcd. for $C_{10}H_{14}ClNO_6S$: C, 38.53; H, 4.53; Cl, 11.37; N, 4.50; S, 10.29. Found: C, 38.40, 38.08; H, 4.39, 4.48; Cl, 11.57. 11.17; N, 4.51, 4.74; S, 10.45, 10.38.

(-)-Ethylmethyl-p-nitrobenzylsulfonium Perchlorate ((-)-21)

A 10.7 g (18.8 mmole) quantity of 27 was dissolved in a minimum amount of methanol and converted as above to its perchlorate (-)-21: m.p. 80°, $[\alpha]^{RT}_{589}$ - 15.4°, $[\alpha]^{RT}_{436}$ - 37.4° (c 0.408, methanol).

p-Chlorobenzyl Alcohol (36)

p-Chlorobenzyl alcohol was prepared in a manner similar to that described by Po (48). p-Chlorobenzaldehyde (150 g, 1.08 mole) in 300 ml. methanol was reduced upon the dropwise addition of a solution of 21.6 g (0.54 mole) sodium borohydride in 100 ml. water. After most of the reducing agent had been added and there was no further evidence of exothermicity, the reaction solution was diluted with 300 ml. water and the mixture extracted with ether twice. The combined extracts were washed with water, dried and concentrated. The solid residue was crystallized from benzene-Skellysolve B solvent mixture to yield 131 g (0.969 mole, 89%) 36: N.M.R. ($CDCl_3$), δ 7.22 (m, 4H), 4.48 (s, 2H), 3.37 (s, 1H); Infrared ($CHCl_3$), 3500 (m), 3300 (broad), 3000(m), 1600 (m), 1500 (s), 1410 (m), 1090 (s) cm^{-1}.

p-Chlorobenzyl bromide (37)

p-Chlorobenzyl bromide was prepared in a manner similar to that described by Po (48). The alcohol 36 (111 g, 0.78 mole) was dissolved in 700 ml. benzene. HBr gas was bubbled through the solution until no more water separated from the solution. The benzene layer was separated, washed successively with water, 5% aqueous sodium bicarbonate and water, dried over magnesium sulfate and concentrated to ca. 150 ml. The solution was diluted with pentane and the mixture cooled to 5° to precipitate 149 g (0.725 mole, 93%) 37: N.M.R. ($CDCl_3$), δ 7.22 (s, 4H), 4.34 (s, 2H); Infrared ($CHCl_3$), 1600 (s), 1490 (s), 1410 (s), 1095 (s) cm^{-1}.

(±)-p-Chlorobenzylethylmethylsulfonium Bromide ((±)-38)

To 26 g (0,127 mole) 37 dissolved in 50 ml. acetone, was added 12 g (0.158 mole) ethyl methyl sulfide. After the solution was allowed to stand at room temperature for 20 hours, it was diluted with 75 ml. and the resulting mixture cooled to - 78°. The oily precipitate was separated, titurated in ether and the residue crystallized under reduced pressure. Recrystallization from methanol-ether solvent mixture gave 20.0 g (0.071 mole, 56%) of the unstable 38: m.p. 87 - 97°; N.M.R. (D_2O, external TMS), δ 7.33 (m, 4H), 4.58 (s, 2H), 3.22 (q, J = 7.5 cps, 2H), 2.74 (s, 3H), 1.34 (t, J = 7.5 cps, 3H); Infrared (nujol), 1590 (w), 1490 (s), 1370 (s), 1095 (s) cm^{-1}.

(±)-p-Chlorobenzylethylmethylsulfonium Perchlorate ((±)-35)

A 19.5 g quantity (0.0693 mole) crude 38 was converted to its perchlorate by anion exchange techniques to yield, after crystallization from methanol, 12 g (0.0398 mole, 58%) (±)-35: m.p. 88 - 89° (reported m.p. 88°(48)); N.M.R. (DMSO-d_6), δ 7.44 (s, 4H), 4.68 (s, 2H), 3.28 (q, J = 7.5 cps, 2H), 2.79 (s, 3H), 1.32 (t, J = 7.5 cps, 3H); Infrared ($CHCl_3$), 1585 (w), 1480 (m), 1085 (s), 610 (m) cm^{-1}.

Anal. Calcd. for $C_{10}H_{14}Cl_2SO_4$: C, 39.88; H, 4.69; Cl, 23.54; S, 10.65. Found: C, 37.83, 37.33; H, 4.53, 4.18; Cl, 22.83, 23.34; S, 10.47, 10.85. In several attempts, the correct analysis for carbon and hydrogen was never achieved. This was likely due to the sample exploding during combustion analysis with accompanying sample loss.

(-)-p-Chlorobenzylethylmethylsulfonium Hydrogen 2(R),3(R)-Dibenzoyltartrate

A 5.06 g sample (16.8 mmole) of (±)-35 was converted to its DBT salt by the usual methods with 6.33 g (16.9 mmole) HDBT. Fractional crystallization of the DBT salt three times from methanol gave the less soluble diastereoisomer 39: m.p. 150 - 151°; $[\alpha]_{589}^{RT}$ - 71.8°, $[\alpha]_{436}^{RT}$ - 174° (c 1.52, methanol) (reported $[\alpha]_{589}^{RT}$ - 69.6° (c 1.6, methanol) (48)); N.M.R. (DMSO-d_6), δ 8.00 - 7.20 (m, 14H), 5.62 (s, 2H), 4.69 (s, 2H), 3.27 (q, J = 7.5 cps, 2H), 2.78 (s, 3H), 1.29 (t, J = 7.5 cps, 3H); Infrared (nujol), 3000 (broad), 1700 (s), 1650 (m), 1590 (w), 1485 (w), 1370 (m) cm^{-1}. To the original mother liquor, concentrated to 75 ml., was added ether to the cloud point and the mixture cooled at 5°. The precipitate, 3.43 g, was recrystallized from methanol to yield 2.25 g of the more soluble diastereoisomer 40: m.p. 150°; $[\alpha]_{589}^{RT}$ - 82.2°; $[\alpha]_{436}^{RT}$ - 198° (c 1.39, methanol).

(R)-(+)-p-Chlorobenzylethylmethylsulfonium Perchlorate ((R)-(+)-35)

A 1.53 g quantity (2.74 mmole) 39 was converted to its perchlorate by anion exchange techniques to yield after two recrystallizations from methanol-ether solvent mixture 0.742 g (2.41 mmole, 90%) (R)-(+)-35: m.p. 80.5 - 81.5°; $[\alpha]_{589}^{RT}$ + 15.0°, $[\alpha]_{365}^{RT}$ + 62.2° (c 0.60, methanol) (reported $[\alpha]_{365}^{RT}$ +56.2° (48)). The Infrared and N.M.R. spectra were superimposible with those of racemic material.

(S)-(-)-p-Chlorobenzylethylmethylsulfonium Perchlorate ((S)-(-)-35)

The more soluble diastereoisomer 40 (2.06 g, 3.67 mmole) was converted to its perchlorate by the usual methods to give 1.00 g (3.33 mmole, 90.7%) (S)-(-)-35: $[\alpha]_{589}^{RT}$ - 38.8° (c 0.936, methanol). Recrystallization of this material from 20 ml. methanol in the freezer gave 0.818 g (-)-35, $[\alpha]_{365}^{RT}$ - 43.5° (c 1.22, methanol). No attempts were made to further increase the optical purity of this isomer.

Nucleophilic Reactions of Ethylmethylsulfonium p-Nitrobenzylid with Carbonyl Compounds

1) with benzaldehyde

A 1.22 g quantity of (3.78 mmole) of 25 was dissolved in a minimum amount of methanol and the solution eluted through an hydroxide exchange column into a flask containing 0.407 g (3.84 mmole) benzaldehyde. The resulting solution, stirred under nitrogen, slowly lost its wine-red colour over a period of one hour. The solvent was removed and the residue crystallized from benzene-pentane solvent mixture to yield 0.608 g (2.48 mmole, 65.5%) trans-p-nitrostilbene oxide (28): m.p. 124° (reported 125 - 126° (30)); N.M.R. ($CDCl_3$), δ 8.23 (d, J = 8.7 cps, 2H), 7.50 (d, J = 8.7 cps, 2H), 7.40 (s, 5H), 3.96 (d, J = 1.6 cps, 1H), 3.83 (d, J = 1.6 cps, 1H); Infrared (nujol), 1602 (w), 1511 (s), 1350 (s), 860 (m), 840 (m) cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.63, 69.12; H, 4.67, 4.74; N, 5.69, 6.16.

2) with p-chlorobenzaldehyde

A 1.26 g quantity (3.91 mmole) of 25 was dissolved in methanol and the solution eluted through an hydroxide column into a flask containing 0.558 g (3.94 mmole) p-chlorobenzaldehyde. After one hour, the solution was concentrated and the residue crystallized from methylene chloride-pentane solvent mixture to yield 0.832 g (3.02 mmole, 77.3%) trans-p-nitro-p'-chlorostilbene oxide (29): m.p. 124 - 125°; N.M.R. ($CDCl_3$), δ 8.26 (d, J = 8.7 cps, 2H), 7.53 (s, J = 8.7 cps, 2H), 7.36 (s, 4H), 3.93 (d, J = 1.6 cps, 1H), 3.84 (d, J = 1.6 cps, 1H); Infrared (nujol), 1600 (m), 1520 (s), 1340 (s), 860 (m) cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}ClNO_3$: C, 60.99; H, 3.65; Cl, 12.86; N, 5.08. Found: C, 61.02, 61.25; H, 3.71, 3.81; Cl, 12.59, 12.63; N, 5.18, 4.98.

3) with p-nitrobenzaldehyde

From 1.22 g (3.77 mmole) 25 and 0.565 g (3.73 mmole) p-nitrobenzaldehyde, was obtained after a single crystallization from methylene-chloride-pentane solvent mixture 0.831 g (2.91,mmole, 77.3%) trans-p,p'-dinitrostilbene oxide (30): m.p. 199 - 200° (reported 200 - 201° (42)); N.M.R. (CD_2Cl_2), δ 8.27 (d, J = 9.0 cps, 4H), 7.56 (d, J = 9.0, cps, 4H), 4.02 (s, 2H); Infrared (nujol), 1600 (s), 1345 (s), 1100 (w), 850 (m) cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.75; H, 3.52; N, 9.79. Found: C, 58.71, 58.69; H, 3.22, 3.44; N, 9.74, 9.97.

4) with acetaldehyde

From 1.26 g (3.90 mmole) of 25 and greater than 2 equivalents excess acetaldehyde was obtained, after a crystallization from methylene chloride-pentane solvent mixture, 0.460 g (2.57 mmole, 66%) trans-1-(p-nitrophenyl)propylene oxide (31): m.p. 86°; N.M.R. (CD_2Cl_2), δ 8.19 (d, J = 9.6 cps, 2H), 7.44 (d, J = 9.6 cps, 2H), 3.66 (d, J = 1.9 cps, 1H), 3.00 (octet, 1H), 1.44 (d, J = 5.2, 3H); Infrared (nujol), 1600 (s), 1345 (s) cm^{-1}.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33, H, 5.06; N, 7.82. Found: C, 59.82, 59.48; H, 5.00, 5.24; N, 7.86, 7.84.

5) with chalcone

In a similar manner, the ylid from 1.21 g (3.76 mmole) of 25 and 0.782 g (3.76 mmole) chalcone were allowed to react for two hours. The evaporation residue was crystallized from benzene-Skellysolve B solvent mixture to obtain a few milligrams of a yellow material, m.p. 199°. The mass and infrared spectra of this material suggested it to be oxirane 30. Mixed melting point determination of this material with the oxirane 30 was undepressed. Addition of more Skellysolve B to the mother liquor precipitated after cooling at - 10° 0.205 g (0.60 mmole, 16%) of a cyclopropane adduct 32: m.p. 104°; N.M.R. ($CDCl_3$), δ 8.25 - 7.25 (m, 14H), 3.80 - 3.00 (m, 3H); Infrared (nujol), 1660 (s), 1600 (s), 1520 (s), 1445 (s), 1345 (s) cm^{-1}. The stereochemistry about the cyclopropane ring was not assigned. The N.M.R. spectrum of the mother liquor showed that decomposition sulfides were present.

6) with ketones

When equimolar quantities of 25 and each of benzophenone, cyclohexanone, p-nitroacetophenone and acetone were treated similarly as for the aldehydes, the colour of the ylid persisted for much longer periods of time. After 7 - 9 hours, the solutions became yellow coloured. The evaporation residues were crystallized from benzene-Skellysolve B solvent mixture to yield in each instance small amounts of 30. The evaporation residues from the mother liquors had similar N.M.R. spectra in the high field region of the spectra. The characteristic absorptions were located at δ 4.16 (q), 2.51 (q), 2.48 (s), 1.95 (s), 1.58 (d) and 1.25 (t). The relative intensity of the doublet to triplet absorptions was ca. 2/1. There were numerous smaller signals in each spectra in the δ 0 - 5 region. Furthermore, a simple para-substitution pattern was not present in the aromatic region of the spectra. No major products could be assigned to oxirane formation from the ketones.

Product Analysis for the Sommelet Rearrangements

1) for ethylmethyl-p-nitrobenzylsulfonium methylsulfate (25)

The evaporation residue of the mother liquor from the reaction of 0.924 g (2.86 mmole) acetone with the ylid 22 from 0.924 g (2.86 mmole) of 25 was chromatographed on 30 g BDH alumina. The column was developed first with 200 ml. pentane and finally with 200 ml. 10% carbon tetrachloride-pentane solvent mixture while collecting the effluent in 25 ml. fractions. The initial fractions of the mixed solvent system after concentration smelled of sulfide. Spotting solutions of these fractions on 5 cm. silica gel thin-layer

chromatographic plates, developing the plates with 10% benzene-cyclohexane solvent mixutre and visualizing the plates with iodine vapour, showed a single spot at be present, R_f = 0.3. However, the first two fractions gave solid evaporation residues whereas the remaining did not. The first two fractions were shown by GLC and N.M.R. spectroscopy to be pure sulfide 34, R_T = 3.7 minutes. The following fractions contained the sulfide 33, R_T = 4.4 minutes, contaminated by small amounts of the sulfide 34. The variable parameters for the GLC analysis were: column, 6' x ¼" 20% SE 30 on 60 - 80 Chromosorb W; column temperature, 210°; detector, 310°; injector, 280°; filament current, 200 ma.; helium flow rate, 60 ml./minute. There was an overlap of the peaks for the two sulfides thereby preventing quantitative analysis. No attempt was made to identify any other compounds of the reaction mixture. Recrystallization of the first two fractions from Skellysolve B gave 34, m.p. 48.5°. The N.M.R. and Infrared spectra of this material were superimposible upon those of a synthetic sample prepared later.

2) for p-chlorobenzylethylmethylsulfonium perchlorate (35)

In a procedure similar to that of Hayashi and Oda for the Sommelet rearrangement of dimethylbenzylsulfonium salts (43), a 1.00 g (3.31 mmole) quantity of 35 was heated for two hours at 70° in a 24% sodium methoxide solution (0.76 g Na (33.1 mmole) in 6.84 g methanol; 10% Na in methanol). The reaction mixture was poured into water and the mixture extracted with ether. The ether extracts were dried and concentrated to give 0.650 g of a yellow oil. The N.M.R. spectrum of

this oil showed only three compounds to be present: methyl α-(2-methyl-5-chlorophenyl)ethyl sulfide (41), ethyl 2-methyl-5-chlorobenzyl sulfide (42) and methyl p-chlorobenzyl ether (43) in the relative ratios of 4.2:1:0.93 respectively. This was confirmed by GLC analysis of the oil: sulfide 41, R_T = 13.2 min.; sulfide 42, R_T = 17.2 min.; ether 43, R_T = 3.76 min. The variable parameters for this GLC analysis were: column, 6' x 3/8" 20% carbowax 1500 on 60 - 80 Chromosorb W; column temperature, 174°; detector, 315°; injector, 270°, collector, 275°; filament current, 200 ma.; helium flow rate, 60 ml./minute.

Bis-chloromethyl Ether

Bis-chloromethyl ether was prepared according to the method of S. R. Buc (50). To a mixture of 84 ml. concentrated HCl (1 mole) and 120 g paraformaldehyde (effectively 4 mole formaldehyde) maintained below 10°, was added dropwise 226 ml. chlorosulfonic acid (3.45 mole) so that no gaseous HCl was lost from the mixture (ca. 5 hours). The mixture was stirred for four hours in an ice-bath, then let stand at room temperature over night. The upper layer was separated, washed with ice-water and with 150 ml. 40% aqueous sodium hydroxide solution. The product was separated, dried over potassium carbonate then potassium hydroxide and the product distilled at atmospheric pressure to yield 144 g bis-chloromethyl ether, b.p. 97 - 99° (700 mm).

2-Methyl-4-nitrotoluene (44)

2-Chloromethyl-4-nitrotoluene was prepared by the method of Berezovskii, Kurdyakova and Proebrazhenskii (49). p-Nitrotoluene (50 g, 0.365 mole) dissolved in 60 ml. bis-chloromethyl ether was treated with 85 g chlorosulfonic acid for one hour below 10°. The solution was allowed to stand overnight at room temperature then treated with ice-water. The precipitate was filtered and recrystallized from methanol to yield 62 g material. This was dissolved in methylene chloride, dried over magnesium sulfate and concentrated. The residue was crystallized from methylene chloride-Skellysolve B to yield 31 g (0.167 g mole, 45.8%) 44; m.p. 67 - 68° (reported m.p. 61.5°); N.M.R. (CD_2Cl_2), δ 8.03 (m, 2H), 7.32 (d, J = 8.0 cps, 1H), 4.63 (s, 2H), 2.50 (s, 3H); Infrared (nujol); 3060 (m), 1612 (m), 1590 (m), 1090 (m), 815 (s), 840 (s), 735 (s) cm^{-1}.

Anal. Calcd. for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; Cl, 19.10; N, 7.55. Found: C, 51.87, 51.99; H, 4.44, 4.20; Cl, 18.90, 19.13; N, 7.49, 7.28.

Ethyl 2-Methyl-5-nitrobenzyl Sulfide (33)

A 12 g quantity (64.5 mmole) 44 in methanol was slowly added to a stirred solution of sodium ethanethiolate prepared by adding 1.54 g (67.0 mmole) sodium and 5 g (80.8 mmole) ethanethiol to 30 ml. methanol. After 30 minutes, the reaction mixture was diluted with 50 ml. water and the resulting mixture extracted with ether several times. The ether extracts were dried over magnesium sulfate and concentrated. The residue was distilled under reduced pressure to yield 10.5 g (49.8 mmole, 77.2%) 33; b.p. 167 - 169° (5 mm); η_D^{25} = 1.5812;

N.M.R. (CD_2Cl_2), δ 7.94 (m, 2H), 7.27 (d, J = 8.0 cps, 1H), 3.77 (s, 2H), 2.51 (q, J = 7.5 cps, 2H), 2.48 (s, 3H), 1.25 (t, J = 7.5 cps, 3H); Infrared (neat), 2980 (m), 2940 (m), 1615 (w), 1590 (m), 1520 (s), 1455 (m), 1350 (s), 1085 (m), 815 (s), 740 (s) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.83; H, 6.20; N, 6.66; S, 15.17. Found: C, 56.56, 57.11; H, 6.16, 6.33; N, 6.77, 6.86; S, 15.16, 15.16.

Ethyl 2-Methyl-5-nitrobenzyl Sulfone (45)

A 0.317 g (1.50 mmole) quantity of sulfide 33 was oxidized upon heating for three hours on a steam bath in the presence of 0.383 g (3.26 mmole) 30% H_2O_2 dissolved in 5 ml. acetic acid. After cooling, the reaction mixture was neutralized with 5% sodium bicarbonate solution and extracted with chloroform. The chloroform extracts were washed with water, dried over magnesium sulfate and concentrated. The solid residue was crystallized from chloroform-Skellysolve B solvent mixture to yield 0.291 g (1.21 mmole, 80.0%) 45: m.p. 139 - 140°; N.M.R. ($CDCl_3$), δ 8.21 - 8.14 (m, 2H), 7.42 (d, J = 7.5 cps, 1H), 4.38 (s, 2H), 3.09 (q, J = 7.0 cps, 2H), 2.57 (s, 3H), 1.45 (t, J = 7.0 cps, 3H); Infrared ($CHCl_3$), 1605 (w), 1580 (w), 1510 (m), 1345 (s), 1310 (s), 1270 (m), 1130 (s), 1110 (s), 1080 (w), 1040 (m), 905 (m), 875 (w) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76; S, 13.18. Found: C, 48.91, 49.11; H, 5.51, 5.46; N, 5.69, 5.58; S, 13.09, 13.17.

2-Cyano-4-nitrotoluene (46)

2-Cyano-4-nitrotoluene was prepared according to the general method described by Vogel (73) for the Sandmeyer preparation of aromatic nitriles. A quantity of 51 g (0.336 mole) 5-nitro-o-toluidine was dissolved in a boiling solution of 85 ml. concentrated HCl and 300 ml. water. The mixture was cooled to 0° in an ice-salt bath. During 15 minutes with vigorous stirring, a solution of 25 g sodium nitrite in 50 ml. water was added to the cooled solution.

A cuprous cyanide solution was previously prepared by adding dilute H_2SO_4 to 100 g copper sulfate pentahydrate in 320 ml. water until the solution was acidic to Congo Red paper. To this solution was added with stirring a solution of 28 g sodium bisulfite in 80 ml. water warmed to 60°, immediately followed by 28 g potassium cyanide in 80 ml. water. After 10 minutes, the cuprous cyanide was filtered and washed with 200 ml. water. The precipitate was transferred to a three litre round bottom and dissolved in a solution of 52 g potassium cyanide in 125 ml. water.

The cuprous cyanide solution was warmed to 60° and the cold diazonium salt solution added slowly with vigorous stirring while maintaining the temperature around 60°. After completion of the reaction, the cooled mixture was extracted three times with ether. The combined ether layers were dried over magnesium sulfate and concentrated. The residue was crystallized from methylene chloride-pentane solvent mixture to yield 37 g (0.228 mole, 68 %) 46; m.p. 97 - 99°, recrystallized from 95% ethanol, m.p. 105 - 106° (reported 106 - 108° (51)); N.M.R. (CD_2Cl_2), δ 8.30 (m, 2H), 7.54 (d, J = 8.5 cps, 1H), 2.67 (s, 3H); Infrared ($CHCl_3$), 2240 (m), 1620 (s), 1590 (s), 1140 (m), 1085 (s), 912 (s), 840 (m) cm^{-1}.

2-Methyl-5-nitrobenzoic Acid (47)

The nitrile 46 was hydrolyzed according to the method of Erlenmeyer, Waldi and Sorkin (52). In a solution of 50 ml. water and 100 ml. concentrated H_2SO_4, 30 g (0.185 mole) 46 was heated at 145° for 6 hours. After cooling, the solution was poured into ice-water and the aqueous layer extracted several times with ether. After clarifying the ether extracts with Norit, the acid was extracted from the ether with 500 ml. of 10% aqueous sodium hydroxide solution. The basic extracts were acidified with HCl to precipitate the crude acid. This was recrystallized from ethanol-water solvent mixture to yield 21 g (0.116 mole, 62.7%) 47; m.p. 178 - 179° (reported 175 - 176° (53)); N.M.R. (DMSO-d_6), δ 8.57 (d, J = 2.6 cps, 1H), 8.28 (q, 1H), 7.57 (d, J = 8.5 cps, 1H), 2.68 (s, 3H); Infrared (nujol), 2700 (broad), 1700 (s), 1520 (s), 1260 (s), 1135 (m), 1075 (m), 740 (m), 690 (m) cm^{-1}.

Anal. Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.90; N, 7.73. Found; C, 52.94, 52.91; H, 3.60, 3.93; N, 7.44, 7.32.

2-Methyl-5-nitrobenzoyl Chloride (48)

A 2.75 g quantity (15.2 mmole) 47 was slowly added in 3 hours to 25 ml of thionyl chloride heated to 60°. The excess solvent was distilled at atmospheric pressure and the traces of solvent removed under reduced pressure. The residue was crystallized from benzene-pentane solvent mixture to yield a small amount of 2-methyl-5-nitrobenzoic anhydride (49). The evaporation residue of the mother liquor was crystallized from benzene-pentane solvent mixture to yield 2.59 g (13.0 mmole, 85.4%) 48; m.p. 55 - 57° (reported 58 - 59° (55)); N.M.R. ($CDCl_3$), δ 9.08 (d, J = 2.5 cps, 1H), 8.42 (q, 1H), 7.57 (d, J =

8.0 cps, 1H), 6.72 (s, 3H); Infrared ($CHCl_3$), 1785 (s), 1760 (s), 1610 (s), 1590 (m), 1530 (s), 1350 (s), 1100 (s), 935 (s), 810 (s).

2-Methyl-5-nitroacetophenone (50)

Crude 48 was prepared by adding 12.4 g (68.5 mmole) 47 to 100 g of refluxing thionyl chloride. Removal of the solvent yielded crude 48 containing a considerable quantity of 49.

Methyl magnesium bromide was prepared by the quantitative conversion of 1.66 g (68.5 mmole) magnesium in 100 ml ether with methyl bromide. After 6.40 g (35.0 mmole) cadmium chloride was added to the Grignard solution at 0°, the mixture was brought to room temperature over 30 minutes. While heating the dimethyl cadmium solution at reflux, an ethereal solution of the crude acid chloride was slowly added over 15 minutes and reflux continued a further 15 minutes. The reaction mixture was poured into ice-water and the layers separated. The ether layer was extracted with aqueous sodium hydroxide solution, water, dried over magnesium sulfate and evaporated. The basic extracts were acidified and filtered to yield 4.33 g (22.4 mmole) 47. The evaporation residue was distilled under reduced pressure to yield 2.00 g (11 mmole, 25%) 50; b.p. 134 - 137°(5 mm); m.p. 54 - 55° (reported 54 - 55° (54)); semicarbazone, from 95% ethanol, m.p. 235 - 236° (reported 222 - 223° (54)); N.M.R. (CD_2Cl_2), δ 8.44 (d, J = 2.5 cps, 1H), 8.14 (q, 1H), 7.40 (d, J = 8.0 cps, 1H), 2.64 (s, 3H), 2.59 (s, 3H); Infrared ($CHCl_3$), 1700 (s), 1620 (s), 1530 (s), 1355 (s), 1100 (m) cm^{-1}.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 59.87, 59.92; H, 5.08, 5.12; N, 7.74, 7.93.

α-(2-Methyl-5-nitrophenyl)ethyl Alcohol (51)

A solution of 0.60 g (15.9 mmole) sodium borohydride in 18 ml. water and 2 ml. of 10% aqueous sodium hydroxide was added dropwise over 45 minutes to a stirred solution of 5.41 g (30.2 mmole) 50 in 50 ml. methanol. The reaction solution was diluted with 100 ml. water and the resulting mixture was extracted with ether several times. The ether extracts were dried over magnesium sulfate and concentrated. The residue was crystallized from chloroform-Skellysolve B solvent mixture to yield 3.29 g (18.2 mmole, 60.4%) 51: m.p. 90 - 91°; N.M.R. (CD_2Cl_2), δ 8.26 (d, J = 2.5 cps, 1H), 7.87 (q, 1H), 7.22 (d, J = 8.0 cps, 1H), 5.11 (q, J = 6.5 cps, 1H), 3.13 (s, 1H), 2.36 (s, 3H), 1.42 (d, J = 6.5 cps, 3H); Infrared ($CHCl_3$), 3600 (m), 1585 (m), 1520 (s), 1450 (m), 1345 (s), 1105 (m), 1065 (m) cm^{-1}.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.64; H, 6.12; N, 7.76. Found: C, 59.57, 59.62; H, 6.35, 6.26; N, 7.72, 7.60.

Methyl 2-Methyl-5-nitrobenzoate (52)

Base catalyzed methanolysis of the acid chloride 48 yielded 52: m.p. 56°; N.M.R. ($CDCl_3$), δ 8.68 (d, J = 2.5 cps, 1H), 8.16 (q, 1H), 7.37 (d, J = 8.0 cps, 1H), 3.93 (s, 3H), 2.68 (s, 3H); Infrared ($CHCl_3$), 1720 (s), 1610 (m), 1520 (m), 1350 (s), 1320 (s), 1130 (s), 1080 (s), 905 (m) cm^{-1}.

α-(2-Methyl-5-nitrophenyl)ethyl Bromide (53)

A 30 ml. benzene solution of 1.27 g (6.98 mmole) 51 was saturated with gaseous HBr. After 30 minutes, the reaction mixture was poured into 150 ml. water and the layers separated. The benzene layer was washed with water, dried over magnesium sulfate and concentrated. The residue was crystallized from Skellysolve B to yield 1.56 g (6.37 mmole, 91.2%) 53: m.p. 53 - 54°; N.M.R. ($CDCl_3$), δ 8.39 (d, J = 2.5 cps, 1H), 8.03 (q, 1H), 7.32 (d, J = 8.4 cps, 1H), 5.38 (q, J = 2.5 cps, 1H), 2.52 (s, 3H), 2.12 (t, J = 7.0 cps, 3H); Infrared ($CHCl_3$), 1605 (w), 1580 (m), 1510 (m), 1240 (s), 1050 (m), 900 (m) cm^{-1}.

Anal. Calcd. for $C_9H_{10}BrNO_2$: C. 44.28; H, 4.13; Br, 32.73; N, 5.76. Found: C, 44.33, 44.07; H, 4.29, 4.21; Br, 32.73, 32.56; N, 5.90, 5.49.

Methyl α-(2-Methyl-5-nitrophenyl)ethyl Sulfide (34)

A 1.49 g quantity (6.10 mmole) of 53 in 25 ml methanol was slowly added to a stirred solution of excess methanethiol and 0.155 g (6.72 mmole) sodium in 25 ml. methanol. After 30 minutes, the reaction solution was diluted with water and the mixture extracted with ether several times. The ether extracts were dried over magnesium sulfate and concentrated. The residue was crystallized from Skellysolve B to yield 1.09 g (5.13 mmole, 84%) 34: m.p. 49.5 - 50.5°; N.M.R. (CD_2Cl_2), δ 8.24 (d, J = 2.4 cps, 1H), 7.96 (q, 1H), 7.25 (d, J = 8.5 cps, 1H), 4.17 (q, J = 7.0 cps, 1H), 2.47 (s, 3H), 1.94 (s, 3H), 1.58 (d, J = 7.0 cps, 1H); Infrared ($CHCl_3$), 1605 (m), 1580 (s), 1500 (s), 1440 (s), 1100 (s), 910 (s) cm^{-1}.

Anal. Calcd. for $C_{10}H_{12}NO_2S$: C, 56.83; H, 6.20; N, 6.66; S, 15.17. Found: C, 56.90, 56.59; H, 6.04, 6.23; N, 6.37, 6.54; S, 15.09, 15.06.

Methyl α-(2-Methyl-5-nitrophenyl)ethyl Sulfone (54)

In a procedure similar to that for the preparation of 45, the sulfide 34 was oxidized to its sulfone 54 in an 80.5% isolated yield: m.p. 150 - 151°; N.M.R..($CDCl_3$), δ 8.38 (d, J = 2.5 cps, 1H), 8.14 (q, 1H), 7.45 (d, J = 8.0 cps, 1H), 4.64 (q, J = 7.0 cps, 1H), 2.85 (s, 3H), 2.59 (s, 3H), 1.87 (d, J = 7.0 cps, 3H); Infrared ($CHCl_3$), 1605 (w), 1580 (w), 1510 (m), 1345 (s), 1310 (s), 1280 (w), 1265 (w), 1135 (s), 1115 (s), 945 (s), 900 (m) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76; S, 13.18. Found: C, 49.20, 49.86; H, 5.44, 5.69; N, 5.35; S, 13.02.

2-Methyl-5-Chlorobenzaldehyde (55)

This was prepared by the method of Jolad and Rajagopal (58). A 10% solution of formaldoxime was prepared by dissolving 11.5 g paraformaldehyde and 26.3 g hydroxylamine hydrochloride in 70 ml. hot water, adding 51 g sodium acetate and refluxing the mixture for 15 minutes. To the resulting solution 6.25 g copper sulfate, 1 g sodium bisulfite and 160 g hydrated sodium acetate in 180 ml. water were added. To 2-methyl-5-chloroaniline (36 g, 0.25 mole) in 57 ml. concentrated HCl and 150 ml. water at 0°, was added dropwise a solution of 17.5 g sodium nitrate in 25 ml. water. After the addition, 22 g hydrated sodium acetate was added to neutralize the solution. The neutral diazonium chloride solution was introduced below the surface of the formaldoxine solution with vigorous stirring at 10 - 15°. Stirring was continued for one hour, then the solution was made neutral to Congo Red paper and a further 230 ml. concentrated HCl added.

The solution was refluxed for 2 hours, then steam distilled. The distillate was neutralized with 5% aqueous sodium bicarbonate and extracted with ether. The ether extract was concentrated to dryness and the residue shaken at 60° with 90 ml. of a 40% aqueous sodium meta bisulfite solution. The addition product was filtered, washed with ether and decomposed in 60 ml 2 N HCl. This hydrolyzed solution was extracted with ether several times. The combined ether extracts were washed with 5% sodium bicarbonate solution, water, dried over magnesium sulfate and concentrated. The residue was crystallized from Skellysolve B to yield 15.2 g (0.0983 mole, 39.3%) 55: m.p. 29 - 31°, sublimed at 30° (0.2 mm), m.p. 31 - 32°; 2,4-DNP, m.p. 250 - 251° (reported 2,4-DNP m.p. 246 - 247° (58)); N.M.R. ($CDCl_3$), δ 10.72 (s, 1H), 7.74 (d, J = 2.0 cps, 1H), 7.43 (q, 1H), 7.17 (d, J = 8.0 cps, 1H), 2.63 (s, 3H); Infrared (nujol), 2610 (m), 1680 (s), 1590 (m), 1555 (w), 890 (s), 820 (s) cm^{-1}.

Anal. Calcd. for C_8H_7ClO: C, 62.15; H, 4.56; Cl, 22.93. Found: C, 61.84, 62.30; H, 4.51, 4.64; Cl, 22.88, 22.96.

2-Methyl-5-chlorobenzyl Alcohol (56)

The aldehyde 55, (13.3 g, 0.0862 mole) in 50 ml. methanol at 20° was reduced by the dropwise addition of a solution of 1.70 g (0.045 mole) sodium borohydride in 20 ml. water. After addition, the reaction mixture was diluted with water and extracted with ether several times. The ether extracts were washed with water, dried over magnesium sulfate and concentrated. The residue was crystallized from benzene-Skellysolve B to yield 11.5 g (0.0735 mole, 85.4%) 56: m.p. 44°; N.M.R. ($CDCl_3$),

δ 7.26 (s, 1H), 7.08 (d, J = 8.0 cps, 1H), 6.99 (d, J = 9.0 cps, 1H), 4.49 (s, 2H), 2.96 (s, 1H), 2.18 (s, 3H); Infrared ($CHCl_3$), 3600 (m), 1600 (m), 1490 (s), 1100 (m), 880 (m) cm^{-1}.

Anal. Calc. for C_8H_9ClO: C, 61.35; H, 5.79; Cl, 22.64. Found: C, 61.66, 61.54; H, 5.57, 6.10; Cl, 22.18, 22.90.

2-Methyl-5-chlorobenzyl Bromide (57)

HBr gas was bubbled through a 50 ml. benzene solution of 56 (11.3 g, 0.0723 mole) until no further water separated. The reaction mixture was poured into water and extracted with benzene several times. The benzene extracts were washed with 5% aqueous sodium bicarbonate solution, water, dried over magnesium sulfate and concentrated. The residue was crystallized from benzene-Skellysolve B solvent mixture to yield 13.9 g (0.0632 mole, 87.5%) 57; m.p. 31 - 32°; N.M.R. ($CDCl_3$), δ 7.26 (s, 1H), 7.18 (d, J = 7.5 cps, 1H), 7.08 (d, J = 7.5 cps, 1H), 4.41 (s, 2H), 2.35 (s, 3H); Infrared ($CHCl_3$), 1600 (m), 1575 (w), 1145 (w), 1110 (s), 900 (s) cm^{-1}.

Ethyl 2-Methyl-5-chlorobenzyl Sulfide (42)

The bromide 57 (12.9 g, 0.0587 mole) in 100 ml. methanol was slowly added to a stirred sodium ethanethiolate solution prepared by adding 1.44 g (0.0626 mole) sodium metal and 4 g ethanethiol to 40 ml. methanol. After one hour stirring, the reaction solution was diluted with 100 ml. water and the resulting mixture extracted with ether several times. The ether extracts were washed with water, dried over magnesium sulfate and concentrated. The residue was distilled under reduced pressure to yield 8.00 g (0.0399 mole, 68.2%) 42; b.p. 117 - 118° (6 mm); η_D^{30} = 1.5611; N.M.R. ($CDCl_3$), δ 7.24 -

6.99 (m, 3H), 3.64 (s, 2H), 2.46 (q, J = 7.5 cps, 2H), 2.34 (s, 3H), 1.23 (t, J = 7.5 cps, 3H); Infrared (neat), 2985 (s), 2965 (s), 1595 (m), 1485 (s), 1400 (m), 1265 (m), 1115 (m), 900 (m), 885 (m), 815 (s) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}ClS$: C, 59.84; H, 6.53. Found: C, 59.97, 59.68; H, 6.79, 6.64.

Ethyl 2-Methyl-5-chlorobenzyl Sulfone (58)

In a procedure similar to that for the preparation of the nitrosulfones 45 and 54, the chlorosulfide 42 was oxidized to its corresponding sulfone 58: m.p. 116 - 117°; N.M.R. ($CDCl_3$), δ 7.28 (m, 3H), 4.23 (s, 2H), 3.00 (q, J = 7.5 cps, 1H), 2.42 (s, 3H), 1.41 (t, J = 7.5 cps, 3H); Infrared ($CHCl_3$), 2970 (w), 1590 (w), 1475 (m), 1310 (s), 1120 (s), 890 (m) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}ClO_2S$: C, 51.61; H, 5.63; Cl, 15.23; S, 13.78. Found: C, 51.77, 51.31; H, 5.68, 5.57; Cl, 15.46, 15.35; S, 13.93, 13.81.

Acetaldoxime

Acetaldoxime was prepared according to the method of Wieland (61). To a solution of 175 g hydroxylamine hydrochloride and sodium carbonate in 450 ml. water at 0°, was added slowly 100 g acetaldehyde in 50 ml. water. After 15 hours at 0°, the solution was saturated with salt and the mixture extracted with ether. After drying the extracts over magnesium sulfate, the organic layer was fractionally distilled at atmospheric pressure through a Vigreaux column collecting 12 g, b.p. 103 - 109° and 65 g, b.p. 109 - 114° fractions of acetaldoxime.

2-Methyl-5-chloroacetophenone (59)

This was prepared by the method of Beech (59). 2-Methyl-5-chloroaniline (35.5 g, 0.247 mole) was diazotized as previously described for the preparation of the aldehyde 55. The neutralized diazonium salt solution obtained was passed below the surface of a stirred solution of 22.5 g acetaldoxime, 12.5 g copper sulfate, 1 g anhydrous sodium sulfite and 165 g sodium acetate in 200 ml. water at 10 - 15°. After the addition, the stirring was continued for one hour, then the solution was made acidic to Congo Red paper and a further 230 ml. concentrated HCl added. The resulting mixture was refluxed for three hours then steam distilled. The distillate was neutralized with 5% sodium bicarbonate solution and extracted with ether. The ether extracts were washed with 10% aqueous sodium hydroxide solution, water, dried over magnesium sulfate and concentrated. The residue was fractionally distilled through a vigreux column under reduced pressure to yield 11.4 g (0.0676 mole, 27.4%) 59; b.p. 94 - 96° (4.5 mm); η_D^{30} = 1.5462 (reported b.p. 121 - 122° (7 mm); η_D^{30} = 1.5452 (60)); 2,4 DNP m.p. 183 - 184°; N.M.R. ($CDCl_3$), δ 7.60 (d, J = 2.0 cps, 1H), 7.27 (q, 1H), 7.10 (d, J = 8.0 cps, 1H), 2.53 (s, 3H), 2.45 (s, 3H); Infrared (neat), 1685 (s), 1595 (w), 1480 (m), 1355 (s), 1285 (s), 1240 (s), 1100 (m), 955 (m), 840 (m), 820 (m) cm^{-1}.

α-(2-Methyl-5-chlorophenyl)ethyl Alcohol (60)

To 6.82 g (0.0405 mole) 59 in 50 ml. methanol at room temperature was slowly added a solution of 0,746 g (0.0197 mole) sodium borohydride in 2 ml. 10% aqueous methanol and 18 ml. water. The reaction solution was poured into 50 ml. 2 N H_2SO_4 and the mixture extracted with ether.

The ether extracts were washed with water, dried over magnesium sulfate and concentrated. The residue was distilled under reduced pressure to yield 5.66 g (0.0332, 82.2%) 60: b.p. 97 - 98° (3.5 mm); η_D^{30} = 1.5457, N.M.R. ($CDCl_3$), δ 7.48 (d, J = 1.5 cps, 1H), 7.08 (m, 2H), 5.04 (q, J = 6.5 cps, 2H), 2.26 (s, 3H), 2.12 (s, 1H), 1.38 (d, J = 6.5 cps, 3H); Infrared ($CHCl_3$), 3600 (m), 1595 (m), 1400 (m), 1375 (m), 1105 (s), 1075 (s) cm^{-1}.

Anal. Calcd. for $C_9H_{11}ClO$: C, 63.35; H, 6.50; Cl, 20.78. Found: C, 63.16, 63.63; H, 6.42, 6.64; Cl, 21.01, 21.27.

α-(2-Methyl-5-chlorophenyl)ethyl Bromide (61)

HBr gas was bubbled through a 10 ml. benzene solution of 1.62 g (9.52 mmole) 60 until no further water separated. The mixture was poured into water and extracted with benzene several times. The extracts were washed with 5% sodium bicarbonate solution, water, dried over magnesium sulfate and concentrated. The residue was distilled under reduced pressure to yield 1.59 g (6.78 mmole, 71.3%) 61: b.p. 94° (3.5 mm); η_D^{30} = 1.5720; N.M.R. ($CDCl_3$), δ 7.49 (d, J = 1.4 cps, 1H), 7.10 (m, 2H), 5.31 (q, J = 6.5 cps, 1H), 2.35 (s, 3H), 2.03 (d, J = 6.5 cps, 3H); Infrared (neat), 2980 (m), 1590 (m), 1480 (s), 1450 (m), 1185 (s), 860 (s), 810 (s) cm^{-1}.

Methyl α-(2-Methyl-5-chlorophenyl)ethyl Sulfide (41)

The bromide 61 (1.63 g, (6.93 mmole) was added to a stirred sodium methanethiolate solution at 0°, prepared by dissolving 0.169 g (7.33 mmole) sodium metal and 1 ml. methanethiol in 10 ml. methanol. After stirring for ½ hour, the reaction solution was poured into water and the mixture extracted with ether. The ether extracts were dried over magnesium sulfate and concentrated. The residue was distilled under reduced pressure to yield 1.02 g (5.08 mmole, 73.5%) 41; b.p. 108 - 110° (5 mm); η_D^{25} = 1.5640; N.M.R. ($CDCl_3$), δ 7.42 (s, 1H), 7.05 (m, 2H), 4.08 (q, J = 6.5 cps, 1H), 2.33 (s, 3H), 1.94 (s, 3H), 1.55 (d, J = 6.5 cps, 3H); Infrared (neat), 2985 (m), 2920 (m), 1595 (m), 1484 (s), 1450 (s), 1125 (m), 865 (s), 810 (s) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}ClS$: C, 59.83; H, 6.52; Cl, 17.66; S, 15.97. Found; C, 59.90, 59.92; H, 6.69, 6.59; Cl, 17.37, 17.86; S, 15.89, 15.79.

Methyl α-(2-Methyl-5-chlorophenyl)ethyl Sulfone (62)

In a procedure similar to that for the preparation of the sulfone 58, the sulfide 41 was oxidized to its sulfone 62: m.p. 143 - 144°; N.M.R. ($CDCl_3$), δ 7.70 (s, 1H), 7.36 (s, 2H), 4.58 (q, J = 7.0 cps, 1H), 2.78 (s, 3H), 2.46 (s, 3H), 1.78 (d, J = 7.0 cps, 3H); Infrared ($CHCl_3$), 2900 (w), 1590 (w), 1480 (m), 1300 (s), 1130 (s), 945 (s), 860 (m) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}ClO_2S$: C, 51.61; H, 5.63; Cl, 15.23; S, 13.78. Found: C, 51.70, 51.53; H, 5.75, 5.61; Cl, 14.95, 15.11; S, 13.97, 13.91.

p-Chlorobenzyl Methyl Ether (43)

A 6.5 g quantity (0.0317 mole) p-chlorobenzyl bromide (37) was added to a sodium methoxide solution (1 g sodium metal in 30 ml. methanol) and the mixture refluxed for 2 hours. The reaction mixture was poured into water and the mixture extracted with ether several times. The ether extracts were washed with water, dried over magnesium sulfate and concentrated. The residue was distilled under reduced pressure to yield 4.24 g (0.0271 mole, 85.7%) 43; b.p. 70 - 71° (10 mm); η_D^{30} = 1.5190; N.M.R. ($CDCl_3$); δ 7.34 (s, 4H). 4.45 (s, 2H), 3.41 (s, 3H); Infrared (neat), 1600 (w), 1490 (s), 1410 (w), 1380 (w), 1195 (w), 1090 (s), 1020 (m), 810 (m) cm^{-1}.

Anal. Calcd. for C_8H_9ClO: C, 61.35; H, 5.79; Cl, 22.64. Found: C, 61.62, 61.65; H, 5.74, 6.03; Cl, 22.62, 22.53.

Asymmetric Induction Experiments

1) Ethylmethylsulfonium p-nitrobenzylid with benzaldehyde

A 0.414 g quantity (1.33 mmole) (-)-21, $[\alpha]_{436}^{RT}$ - 37.7° (c 0.408, methanol), was dissolved in a minimum amount of methanol and eluted through an hydroxide exchange column into a flask containing 0.1487 g (1.40 mmole) benzaldehyde. The solution was stirred under N_2 for one hour then concentrated. The residue, 0.310 g, had a specific rotation of $[\alpha]_{546}^{RT}$ + 6.37° (c 1.24, CH_2Cl_2). This was crystallized from methylene chloride-Skellysolve B solvent mixture to yield 0.184 g (0.76 mmole, 57%) racemic oxirane 28. The mother liquor was concentrated to yield 0.151 g material, $[\alpha]_{546}^{RT}$ + 12.2° (c 3.02, CH_2Cl_2). This latter residue was triturated in pentane to crystallize 0.063 g (0.26 mmole, 20%) (+)-28; m.p. 125°; $[\alpha]_{546}^{RT}$ + 5.53° (c 0.506, benzene). The N.M.R.

spectrum of the active oxirane was superimposible upon that of racemic material. After concentration of the mother liquor from the latter crystallization, the N.M.R. spectrum of the residue indicated the presence of 28 as well as decomposition products including sulfide 34. A final 9 mg of solid material, m.p. 120 - 122 , $[\alpha]^{RT}_{546}$ + 20 (c 0.18, benzene) was obtained by trituration of the residue in Skellysolve B.

2) Ethylmethylsulfonium p-nitrobenzylid with acetaldehyde

In a similar manner, 0.672 g (2.16 mmole) (+)-21, $[\alpha]^{RT}_{436}$ + 41.4° (c 0.459, methanol), was dissolved in a minimum amount of methanol and eluted through an hydroxide exchange column into 6 g acetaldehyde at 0°. The wine-red colour of the ylid disappeared almost immediately. The solvent was removed and the residue crystallized from benzene-pentane solvent mixture to yield 0.194 g (1.08 mmole, 50.2%) racemic 31. When the evaporation residue of this crystallization was titurated in hot Skellysolve B and the mother liquor decanted from a red residue and cooled at 5°, 0.0774 g (0.43 mmole, 20%) (-)-31: m.p. 85 - 86°; $[\alpha]^{RT}_{436}$ - 4.9° (c 0.77, benzene), was isolated. The red residue, optically active (-), was shown by N.M.R. spectroscopy to contain some epoxide 31 plus decomposition products including sulfide 34.

3) Rate of change of optical activity of (+)-ethylmethylsulfonium p-nitrobenzylid

A 0.555 g quantity of 21, $[\alpha]^{RT}_{436}$ + 38.2° (c 0.385, methanol) was dissolved in 40 ml. methanol and passed through an hydroxide exchange column into a 100 ml. volumetric flask. Aliquots of this solution were transferred to polarimeter cells thermostated at 25° and 50°. The changes of rotation observed on the sodium D line are given in Table IX.

TABLE IX

RATE OF CHANGE OF OPTICAL ACTIVITY OF (+)-ETHYLMETHYLSULFONIUM p-NITROBENZYLID[a]

25°		50°	
Time, sec.	α_{589},°	Time, sec.	α_{589},°
0	0.077	1350	0.060
1750	0.085	1500	0.072
7225	0.091	1900	0.083
10150	0.084	2850	0.081
15350[b]	0.076	7175[b]	0.052
28500	0.062	8900	0.044
42200	0.056	12650	0.034
78000	0.049	42150	0.028
100900	0.030	100900	0.028
	0.028		

a: Effluent solution from 0.555 g 21, $[\alpha]_{436}^{RT}$ + 38.2° (c 0.385, methanol).

b: Wine-red colour of ylid disappeared.

4) Sommelet rearrangement of Ethylmethyl-p-nitrobenzylsulfonium perchlorate ((+)-21)

A 1.01 g quantity (3.23 mmole) of 21, $[\alpha]_{436}^{RT}$ + 34.7° (c 1.06, methanol), was dissolved in methanol and eluted through an hydroxide exchange column into a 250 ml. volumetric flask. After nine hours at room temperature, a 49.93 ml. aliquot of the effluent solution and a 4.890 ml. aliquot of a solution of 1.422 g benzhydrol (8.0 mmole) in 100 ml. benzene were mixed and the solution concentrated.

Using the integrations of the benzylic protons of sulfide 33, the S-methyl protons of sulfide 34 and the benzylic proton of benzhydrol in the N.M.R. spectrum of the evaporation residue, the yields of the two sulfides 34 and 33 were estimated to be 30% and 12% respectively. This analysis is summarized in Table X.

TABLE X

N.M.R. PRODUCT ANALYSIS OF THE SOMMELET REARRANGEMENT OF ETHYLMETHYL-p-NITROBENZYLSULFONIUM PERCHLORATE[a]

Compound	Ave. Integ.	# Protons	Mmole/Analysis	Yield, mmole, %
benzhydrol	1.95	1 benzylic	0.391	
sulfide 34	2.90	3 S-methyl	0.194	0.97, 30
sulfide 33	0.79	2 benzylic	0.076	0.38, 12

a: theoretical yield of products per analysis, 1/5 of 3.23 mmole (+)-21.

Crude (+) sulfide 34, $[\alpha]^{RT}_{589}$ + 19.7°, $[\alpha]^{RT}_{578}$ + 20.1°, $[\alpha]^{RT}_{436}$ + 42.7° (c 0.483, CH_2Cl_2) was isolated from the remaining reaction mixture by chromatography of the evaporation residue in a manner analagous to the isolation of the pure racemic sulfide. Crystallization of the crude from Skellysolve B gave sulfide (+)-34, $[\alpha]^{RT}_{436}$ + 39.1° (c 0.358, CH_2Cl_2). This material was pure by GLC. analysis. Its N.M.R. and Infrared spectra was superimposible with those for racemic material. Assuming the absolute rotation of 21 to be $[A]^{RT}_{436}$ 41.4°

(c 0.459, methanol), the highest specific rotation recorded, the corrected rotation for the non-crystallized sulfide obtained for this experiment was $[\alpha]^{RT}_{436}$ + 51.0° (c 0.483, CH_2Cl_2).

In a similar experiment, the 250 ml. solution of the ylid 22 derived from 1.01 g (3.23 mmole) (+)-21, $[\alpha]^{RT}_{436}$ + 40.3° (c 0.94, methanol), was let stand at room temperature for 17 hours. A 150 ml. portion of this solution was concentrated to dryness and the residue chromatographed on 22 g Woelm neutral alumina (activity one) with benzene-Skellysolve B solvent mixtures to give 0.0512 g (0.242 mmole) non-crystallized (+)-34, $[\alpha]^{RT}_{436}$ + 54.2° (c 0.512, CH_2Cl_2), corrected +55.6°. Oxidation of this latter crude (+)-34 with 0.103 g (0.91 mmole) 30% H_2O_2 in a manner described for the preparation of the racemic sulfone 54, gave after workup 0.0567 g (0.233 mmole, 96.5%) non-crystallized (+)-54: $[\alpha]^{RT}_{436}$ + 31.6° (c 0.567, $CHCl_3$). The N.M.R. spectrum of this material was superimposible upon that of its racemate.

5) Sommelet rearrangement of (R)-(+)-p-chlorobenzylethylmethylsulfonium perchlorate ((R)-(+)-35)

A 0.502 g quantity of (R)-(+)-35, $[\alpha]^{RT}_{546}$ + 16.2° (c 0.566, methanol), was treated with sodium methoxide in a procedure similar to that described for its racemate. The evaporation residue after workup was transferred to a 5 ml. volumetric flask with benzene and analyzed for optical rotation, α^{RT}_{589} + 1.17°, α^{RT}_{436} + 2.44°. Using the product yield determined later, the specific rotation of the active sulfide 41 was $[\alpha]^{RT}_{589}$ + 32.3°, $[\alpha]^{RT}_{436}$ + 67.4° (c 3.62, benzene).

The product balance for this rearrangement was determined by GLC using the column and conditions outlined earlier for the analysis of the racemate. An accurately known amount of the internal standard, 2-methylnaphthalene, R_T = 7.40 minutes, was added to each injection solution in order to ascertain the percentage yields of each component. In order to calibrate the analytical method, a series of standard solutions for each component of various concentrations were prepared by making a series of dilutions of a stock solution of each in benzene as shown in Table XI. Control solutions in serum-capped vials were prepared by transferring 1.014 ml. of each of these standard solutions by means of a calibrated automatic pipette to 1.014 ml. aliquots of a 2-methylnaphthalene stock solution. A typical stock solution of the internal standard was prepared by dissolving 0.314 g 2-methylnaphthalene in benzene in a 25 ml. volumetric flask. The series of control solutions containing various ratios of each component relative to the internal standard were injected into the GLC in 20 μl. aliquots and the area of each component relative to the peak area of the internal standard was calculated using the Honeywell Disc Chart Integrator. The weight ratios and observed area ratios of the control solutions are listed in Table XII. Standardization curves were constructed by plotting the area ratio versus weight ratio as illustrated in Figure XIV for the case of sulfide 41. The slope of the line was determined by using a least squares program available for an Olivetti Programme 101 Electronic Desk Computor.

A 1.014 ml. aliquot of a stock solution of the internal standard and a 1.014 ml. aliquot of the optical analysis solution were mixed and three 20 μl. samples of the resulting solution were injected into

TABLE XI

STANDARD SOLUTIONS FOR THE PRODUCT ANALYSIS OF THE SOMMELET REARRANGEMENT OF (R)-(+)-p-CHLOROBENZYLETHYLMETHYLSULFONIUM PERCHLORATE

Solution	Aliquots of Stock[a] ml.	Aliquots of Benzene ml.	Dilution Factor
A	1 x 1.014	0	1.00
B	4 x 1.014	1 x 1.014	0.80
C	3 x 1.014	1 x 1.014	0.75
D	2 x 1.014	1 x 1.014	0.67
E	1 x 1.014	1 x 1.014	0.50
F	1 x 1.014 of C	1 x 1.014	0.375
G	1 x 1.014	4 x 1.014	0.20

a: Stock solution of sulfide 41, 1.6536 g / 25 ml. benzene; of sulfide 42, 0.4068 g / 25 ml. benzene; of ether 43, 0.3366 g / 25 ml. benzene.

TABLE XII

CONTROL ANALYSES OF THE PRODUCTS OF THE SOMMELET REARRANGEMENT OF (R)-(+)-p-CHLOROBENZYLETHYLMETHYLSULFONIUM PERCHLORATE

Control	Weight and Area Ratios of Substrate / Standard					
	sulfide 41		sulfide 42		ether 43	
	weight	area	weight	area	weight	area
A	5.55	4.92	1.344	1.137	1.088	1.042
B	4.45	3.95	1.075	0.966	0.870	0.832
C	4.16	3.78	1.008	0.877	0.816	0.756
D	3.70	3.27	0.897	0.784	0.725	0.715
E	2.77	2.49	0.672	0.572	0.544	0.598
F	2.09	1.84	0.504	0.496	0.408	0.406
G	1.11	1.00	0.269	0.201	0.218	0.259
SLOPE[a]	0.889		0.861		0.885	

a: From the calibration curves plotting area ratios versus weight ratios.

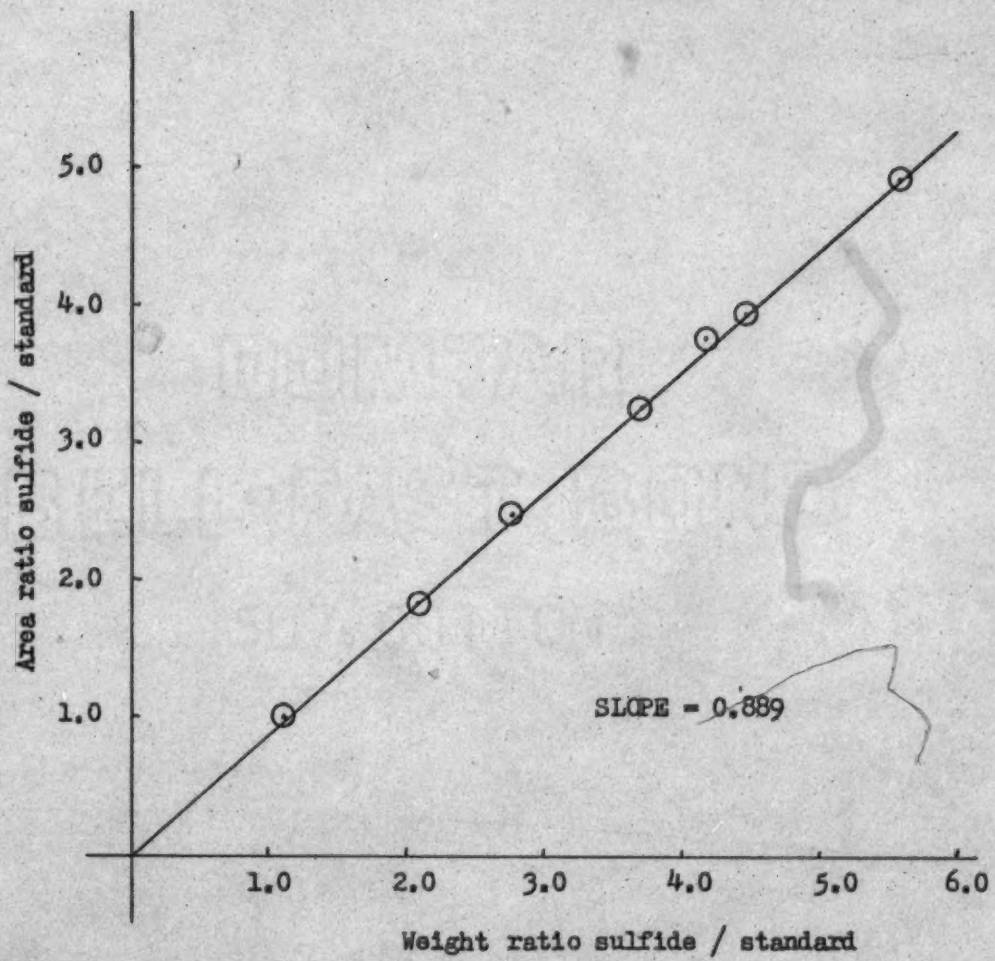


Figure XIV. Calibration curve for methyl α-(2-methyl-5-chlorophenyl)-ethyl sulfide (41) using 2-methylnaphthalene as an internal standard.

the GLC. The area of each component relative to the peak area of the internal standard was calculated. Knowing the slope, the area ratio of the component and the standard, and the weight of the internal standard, it was possible to calculate the weight of each component analyzed in each injection solution and hence the weight of each component in the bulk sample. Table XIII summarizes the results of these experiments to determine the product balance.

The optical analysis solution remaining after GLC analysis was concentrated and the residue dissolved in a small amount of benzene was injected into the GLC in 20 μl. aliquots. The gases corresponding to the desired active sulfide (+)-41 were condensed in a U-tube fitted into the collection port of the GLC instrument. The condensate, $[\alpha]^{RT}_{589}$ + 31.1°, $[\alpha]^{RT}_{436}$ + 66.2° (c 0.660, benzene), had N.M.R. and Infrared spectra identical with those for racemic material.

In a similar experiment, 0.504 g (1.67 mmole) (R)-(+)-35, $[\alpha]^{RT}_{546}$ + 16.2° (c 0.566, methanol), was treated with sodium methoxide. The evaporation residue after workup was dissolved in benzene in a 25 ml. volumetric flask. A concentrated benzene solution of the evaporation residue from 15 ml. of this solution was injected into the GLC in 20 μl. aliquots. The gases corresponding to the active sulfide (+)-41 were condensed. The condensate, $[\alpha]^{RT}_{436}$ + 70.8° (c 0.26, benzene), was oxidized with excess H_2O_2 as described previously for the oxidation of the racemic sulfide to give the sulfone (+)-62, $[\alpha]^{RT}_{365}$ + 26.9° (c 0.29, benzene). The N.M.R. spectrum of this non-crystallized material was superimposible upon that of its racemate.

TABLE XIII

PRODUCT YIELDS FOR THE SOMMELET REARRANGEMENT OF (R)-(+)-p-CHLORO-BENZYLETHYLMETHYLSULFONIUM PERCHLORATE[a]

Compound	Area Ratio[b]	Mg / Analysis[c]	Total Yield, mmole	Average Yield, %
41	2.54	36.4	0.90	
	2.63	37.7	0.93	53.9
	2.51	36.0	0.89	
42	0.542	8.03	0.20	
	0.599	8.87	0.22	12.6
	0.579	8.57	0.21	
43	0.983	14.2	0.45	
	1.073	15.5	0.49	27.6
	0.984	14.2	0.45	
		Total recovery = 94.1% of theory		

a: Analysis solution contains 12.75 mg 2-methylnaphthalene as internal standard and 1.014/5 of the products from the rearrangement of 1.67 mmole (R)-(+)-35.

b: Product/standard area ratios from GLC analysis.

c: Calculated knowing the slopes from Table XII for the calibration curves.

CHAPTER FOUR

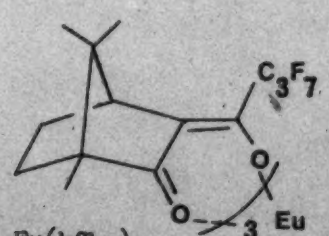
ESTIMATION OF ASYMMETRIC INDUCTION IN THE SOMMELET REARRANGEMENTS

Introduction

As indicated earlier, the extent of asymmetric synthesis in a reaction is directly related to the optical or enantiomeric purity of the product formed. Although enantiomeric purity and optical purity give the same information about an enantiomeric mixture and hence can be used interchangebly, a distinction between the two will be maintained in this chapter because of the inherently different experimental methods used to determine each. The task was therefore to determine the optical and enantiomeric purity of the active Sommelet sulfides (+)-34 and (+)-41.

Enantiomeric Purity of the Sommelet Sulfides

Of the N.M.R. methods available to determine the enantiomeric purity of a compound, the techniques involving chiral shift reagents give accurate data with the least amount of experimental time. The chiral lanthanide shift reagent Tris[3-(heptafluorobutyryl)-d-camphorato]-europium(III), commonly abbreviated as $Eu(hfbc)_3$, has been reported to cause differential downfield shifts (LIS) in the N.M.R. spectra of numerous racemates containing functional groups such as amines, alcohols, esters, ketones, epoxides, sulfoxides and aldehydes (74).



$Eu(hfbc)_3$

When a $CDCl_3$ stock solution of $Eu(hfbc)_3$ was added to a solution of either of the racemic Sommelet sulfides 34 or 41, no spectral shifts were observed in the N.M.R. spectra. However, when the reagent was added to solutions of their corresponding sulfones 54 and 62, spectral shifts were observed with the enantiotopic groups giving distinguishable resonances. At the appropriate molar ratios of shift reagent to sulfone, the S-methyl and α-methyl resonances for each enantiomer were separated sufficiently such that the relative areas of the resonances for each enantiotopic group could be determined by integration using a Varian HA 100 Analytical Spectrometer. Hence, for the active sulfones, the enantiomeric purity could be obtained from the relative integrations of the resonances of enantiotopic methyl groups. It was found that the enantiomeric purity of the sulfones could be determined without having to isolate the sulfides in a pure state from the crude reaction product. When the reaction product was oxidized with excess H_2O_2 in acetic acid at 100°, the extraneous compounds in the oxidized mixture were found not to interfere with the N.M.R. analysis of the active sulfones. Fortutiously, the by-products such as the ethyl sulfones 45 and 58, ethers and other compounds in each mixture, did not have spectral absorptions coincident with the enantiotopic resonances studied when the shift reagent was added. Obviously, the accurate estimation of enantiomeric purity using enantiotopic resonances requires that no extraneous signals be buried under the signals studied thereby biasing the relative ratio of the integration.

N.M.R. spectral shifts were also observed for the pure ethyl sulfones 45 and 58 in the presence of $Eu(hfbc)_3$. As the hydrogens of the methylene groups in the benzyl and ethyl portions of the molecule were prochiral, they became diastereotopic to one another under the influence of the chiral shift reagent with the result that small differential shifts between the pro-R and pro-S hydrogens were observed. Similar differential N.M.R. resonance signals have been observed for the internally enantiotopic protons of dibenzyl sulfone (75).

The results of the chiral shift experiments to determine the enantiomeric purity of the active sulfones derived from the Sommelet rearrangements, as outlined in detail in the experimental section, are: nitro-sulfone 54, 19.5 ± 0.7% (isolated) and 20.3 ± 0.7% (crude); chloro-sulfone 62, 27.0 ± 1.2% (isolated) and 25.5 ± 0.4% (crude). The term "isolated" refers to non-fractionally crystallized sulfones obtained from pure sulfides isolated from the product mixtures of the Sommelet rearrangements described in Chapter Three. The term "crude" refers to the sulfone present in the oxidized product mixture obtained as described in the experimental section of this chapter. The errors reported with these numbers are the average deviation from the mean of six determinations. The agreement between the analyses for the isolated sulfones and those for the crude sulfones verifies that there were no extraneous signals buried under the enantiotopic resonances that were used to estimate the relative amounts of each enantiomer. The enantiomeric purity of the sulfides was taken to be identical with their sulfones, as racemization during the oxidation of the sulfides in the acid medium was considered

unlikely. It has been shown, however, that chiral centers adjacent to sulfonyl functions racemize under base-catalyzed conditions via α-sulfonyl stabilized carbanion (76).

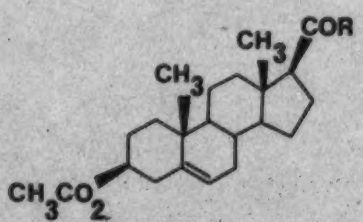
In order to verify these estimations of enantiomeric purity, an independent method of analysis was required. To accomplish this, work was initiated simultaneously to prepare the resolved Sommelet sulfides and sulfones. The optical purity of the sulfides isolated from the Sommelet rearrangements could then be determined by comparison of the observed specific rotations with the absolute rotations of the pure enantiomers.

Preparation of Optically Active Methyl α-(2-Methyl-5-nitrophenyl)ethyl Sulfide (34)

The synthetic route to the racemic sulfide 34 proceeded via α-(2-methyl-5-nitrophenyl)ethyl alcohol (51). Resolution of this alcohol would then provide the necessary precursor to the active sulfide. 3β-Acetoxy-Δ^5-etienic acid (72) was chosen as a possible agent for the resolution of the alcohol. The acid has had limited but successful usage in resolving alcohols as crystalline diastereomeric esters especially when the salt approach failed (77). In addition to the usual optical methods, it was hoped that N.M.R. spectroscopy might be used to follow the progress of the resolution by monitoring peaks due to diastereotopic groups of the esters.

The acid was readily available by hypobromite oxidation of the commercially available pregnenolone acetate (73) by the method of Staunton and Eisenbraun (78). The resolving acid was converted to its crude acid chloride 74 by reaction with thionyl chloride according

to the method of Steiger and Reichstein (79). Failure to follow their experimental conditions initially resulted in high yields of the corresponding anhydride. The diastereomeric ester mixture was prepared by reaction of the crude acid chloride with the alcohol 51 in pyridine. After workup, small amounts of the anhydride 75 were removed by fractional crystallization from chloroform-Skellysolve B solvent mixture with the ester remaining in the mother liquor. The N.M.R. spectrum of the evaporation residue of the mother liquor indicated the presence of a 50:50 mixture of diastereomeric esters as the angular methyl groups of the steroidal skeleton and the aromatic ortho-hydrogen displayed distinct resonances for each isomer. Crystallization of the residue from benzene-Skellysolve B solvent mixture gave the solid ester 76, m.p. 117 - 118°, $[\alpha]_{436}^{RT}$ - 25.3° (c 0.645, CH_2Cl_2). Unfortunately, repeated crystallization of the ester failed to change the integration ratios of the diastereotopic C-18 methyl groups or to change the sample's specific rotation.



72: R = OH
73: R = CH_3
74: R = Cl
76: R = $OCH(CH_3)Ar$

Though this resolution failed, a method of determining the optical purity of the resolved alcohol once obtained was available. An N.M.R. spectrum of the ester derived from an optically pure sample of the alcohol would exhibit only one signal for a C-18 angular methyl group. This would however provide redundant information with that which could be obtained more easily using the chiral shift reagent $Eu(hfbc)_3$.

The classical method of resolving an alcohol has involved increasing the acidity of an alcohol-containing compound by conversion to an alkyl hydrogen phthalate so preparing an organic acid. Resolution was then accomplished by the fractional crystallization of the diastereomeric salt formed from the acid with a suitable optically active base. This technique was used to resolve the hydrogen phthalate 77 of the alcohol 51 via salt formation with (+) or (-)-α-phenylethyl amine (78). The convenient laboratory preparation of both enantiomers of the amine following the method of Thielacker and Reichstein (80) facilitated the isolation of both enantiomers of the alcohol 51.

The hydrogen phthalate 77 was prepared by reaction of the alcohol 51 with an equimolar quantity of phthalic anhydride in pyridine at 100°. In a typical resolution of the racemate, equimolar amounts of the (-)-amine and (±)-77 were mixed in methanol, then ether added to the solution and the mixture cooled at 5° to precipitate the less soluble diastereoisomer 79, m.p. 167°. In repeated recrystallizations of this first crop, the specific rotations of the material maximized after two crystallizations then began to slowly decrease. However, in several experiments, the hydrogen phthalates (-)-77 obtained from the salts after the specific rotations had maximized, had similar rotations of $[\alpha]_{436}^{RT}$ - 160 to - 165° (c 1.0, $CHCl_3$), even though the salts had specific rotations varying from $[\alpha]_{436}^{RT}$ - 15 to - 19° (c 1.0, methanol). The evaporation residue from the original mother liquor of the less soluble diastereomer was crystallized from ether to give the more soluble diastereoisomer 80, m.p. 150°, $[\alpha]_{436}^{RT}$ ca. 0° (c 1.86, methanol). Regeneration of the hydrogen phthalate from 80 gave (+)-77, $[\alpha]_{436}^{RT}$ + 132° (c 4.4, $CHCl_3$). The optical purity of the

(+) isomer was increased by resolution with (+)-78, enantiomeric with the (-)-amine originally used. Thus the more soluble salt of the (-) amine became the less soluble salt of the (+) amine. Regeneration of the hydrogen phthalate from this salt gave (+)-77, $[\alpha]^{RT}_{436}$ + 164° (c 0.956, $CHCl_3$).

Neither active hydrogen phthalate obtained gave correct analysis though their N.M.R. and Infrared spectra were superimposible upon each other and with those of their racemate. Both isomers occasionally had sharp melting points of 75°, though a depression of 3-4 degrees was usually observed. These problems of analysis and broadened melting points were not overcome despite numerous attempts. The ultimate result was unaffected in that base catalyzed hydrolysis of each isomer yielded the corresponding (+) and (-) alcohols 51 of opposite rotations of $[\alpha]^{RT}_{436}$ 150° (c 0.5, $CHCl_3$). The identity of the specific rotations of the two isomers suggested that 100% optical purity of the alcohols had been achieved despite the problems associated with their hydrogen phthalates.

The optical purity of each enantiomer of 51 was confirmed by observing the downfield N.M.R. spectral shifts for solutions of each isomer upon addition of $Eu(hfbc)_3$. At a molar ration of 0.167 for the shift reagent to (±)-51, the α-methyl group was split into an observed triplet, i. e. overlapping doublets, as observed on a 60 MHz. instrument. When $Eu(hfbc)_3$ was added to solutions of each enantiomer, the duplicity of resonances for the α-methyl group was absent and only a single doublet was observed in each case. No absorptions due to an enantiomeric impurity could be seen in the region of the doublet.

Having resolved the alcohol 51, it was necessary to derivatize it with a suitable leaving group such that a displacement reaction by methanethiolate would provide the desired sulfide 34. In their kinetic study of the Walden inversion reactions of α-phenylethyl chloride, Hughes, Ingold and Scott found varying degrees of S_N1 and S_N2 displacement reactions, with ions of increased nucleophilicity facilitating bimolecular substitution reactions (81). Although the methods of preparing active α-phenylethyl chlorides from alcohols (with thionyl chloride or phosphorous oxychloride) are well known, the stereochemical integrity of the chiral center has not always been maintained (81,82). For these reasons, the preparation of the tosylate of 51 was considered better than that of the corresponding chloride. If the preparation of the tosylate was successful, the overall process from the alcohol to sulfide would involve the chiral center only once. The synthetic route to the resolved sulfide 34 from the racemic alcohol 51 is summarized in Figure XV.

The tosylate 81 was prepared in yields of 20 - 40 % by the reaction of equimolar quantities of 51 with tosyl chloride in pyridine at - 10° for three days. The remainder of the product was the corresponding chloride 82. The yield of tosylate could not be increased beyond 40% despite attempts to alter the reaction conditions. During the reaction, pyridinium hydrochloride precipitated thereby consuming chloride ion which could not react with the tosylate to produce the undesired 82. To ensure that the pyridinium hydrochloride would precipitate, the reaction mixture was seeded with a crystal of the salt. Despite the seeding, considerable yields of the chloride were always obtained.

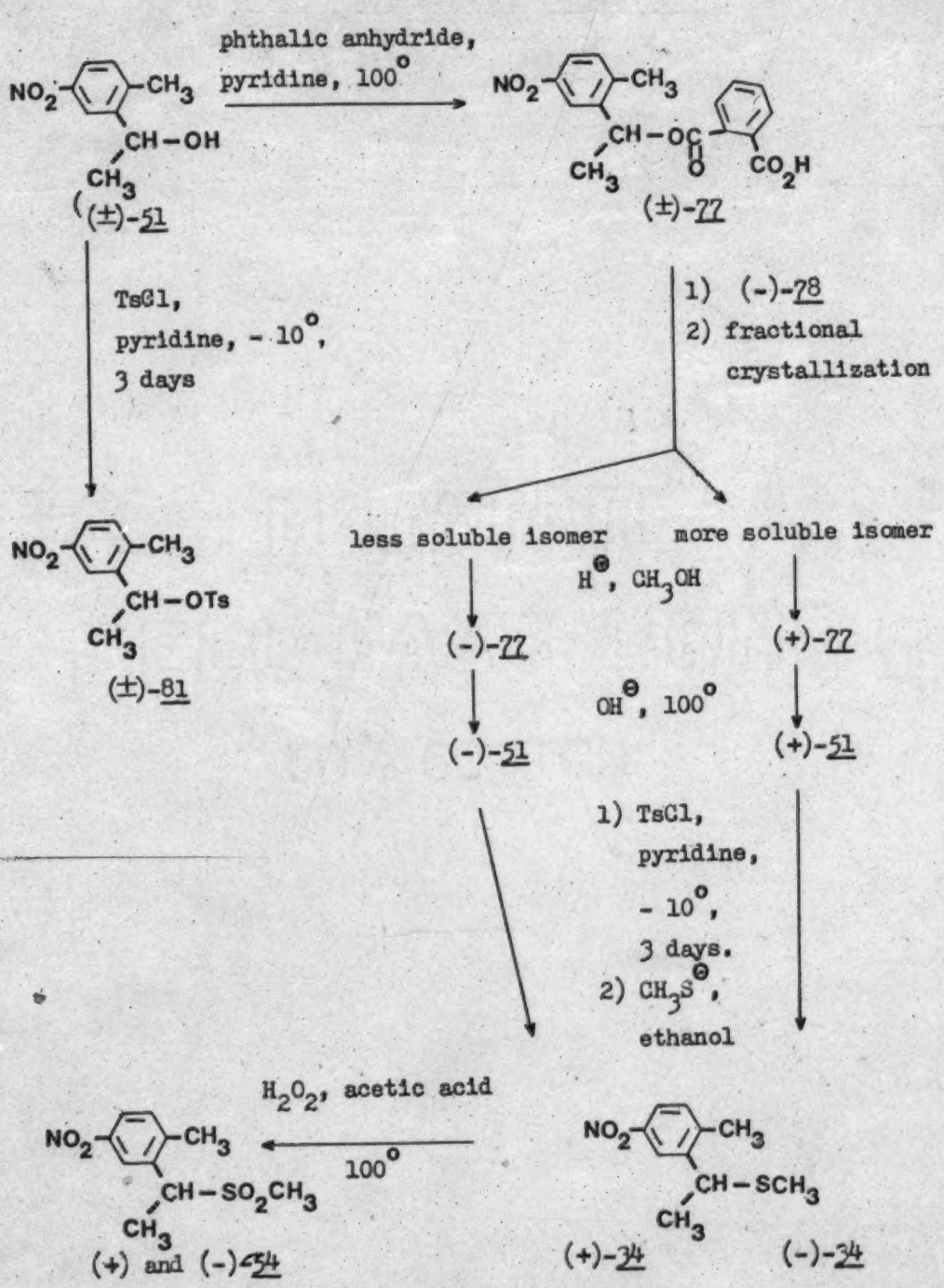


Figure XV. Preparation of optically active methyl α-(2-methyl-5-nitrophenyl)ethyl sulfide and sulfone.

Tosylate of constant rotation, $[\alpha]^{RT}_{436}$ 351° (c 0.5 - 1.2, benzene) for each enantiomer, was obtained by the fractional crystallization of the crude product three times from benzene-Skellysolve B solvent mixture.

Nucleophilic displacement by sodium methanethiolate on the tosylate (-)-81 in ethanol yielded the desired sulfide (+)-34: crude non-crystallized, $[\alpha]^{RT}_{436}$ + 242° (c 0.963, CH_2Cl_2); crystallized, $[\alpha]^{RT}_{436}$ + 266° (c 0.656, CH_2Cl_2). Similarly, the enantiomeric crude non-crystallized sulfide (-)-34, $[\alpha]^{RT}_{436}$ - 256° (c 0.534, CH_2Cl_2), was obtained from the tosylate (+)-81. The sign inversion that occurred in proceeding from the alcohol to sulfide via the tosylate suggested inverted stereochemistry in the sulfide compared to the alcohol or tosylate, as was expected from the published results of the S_N2 reactions of hydroxide, alkoxides and thiolates on optically active α-phenylethyl chloride (81,83).

Oxidation of the sulfide (+)-34, $[\alpha]^{RT}_{436}$ + 266° (c 0.656, CH_2Cl_2), gave after crystallization from $CHCl_3$-Skellysolve B solvent mixture, the corresponding sulfone (+)-54, $[\alpha]^{RT}_{436}$ + 149° (c 0.72, $CHCl_3$). The enantiomeric purity of this sulfone was 86.0 ± 1.0% as determined by N.M.R. spectral shift analysis. The absolute rotation of the sulfone was therefore calculated to be $[A]^{RT}_{436}$ 173°. The maximum specific rotation obtained for (+)-54 was $[\alpha]^{RT}_{436}$ + 155° (c 0.21, $CHCl_3$) after several recrystallizations from benzene. Similarly, oxidation of the sulfide (-)-34, $[\alpha]^{RT}_{436}$ - 256° (c 0.534, CH_2Cl_2), gave the corresponding crude sulfone (-)-54, $[\alpha]^{RT}_{436}$ - 145° (c 0.55, $CHCl_3$). The enantiomeric purity of this sulfone was determined to be 94.1 ± 0.3%. From this figure, the absolute rotation of the sulfone was cal-

culated to be $[A]^{RT}_{436}$ 154°. However, the crude (-)-54 was crystallized to give material, $[\alpha]^{RT}_{436}$ - 163° (c 0.474, $CHCl_3$). The incongruity of these results suggested that weighing errors became significant in the analysis of the crude sulfones. Based on the enantiomeric purity estimation of 94.1% for the crude non-crystallized sulfone (-)-54 and the fact that little optical fractionation occurred upon several recrystallizations of (+)-54, the absolute rotation of 54 was again calculated to be $[A]^{RT}_{436}$ 173°. Assuming the oxidation of the active sulfide 34 did not affect the stereochemical integrity of the α-chiral center and assuming that the tosylates 81 were enantiomerically pure, the less than 100% optical purity for the sulfones 54 indicated that a small amount of the displacement reaction by sodium methanethiolate on 81 proceeded via an S_N1 reaction mechanism.

Typically the crude non-crystallized samples were evaporation residues obtained in 25 or 50 ml. 14/20 ℡ pear-shaped flasks. The weight of the crude was determined from the difference in the weight of the flask plus crude and the weight of the flask after the crude had been washed from the flask with solvent and the excess of solvent removed under reduced pressure. Although the flasks were handled with tongs and tissue paper during this process, weighing errors apparently arose. The weights of the crystallized materials were considered more reliable as the solids were easily transferred unto tared weighing papers then quantitatively transferred to volumetric flasks. The correlations with crystallized rather than non-crystallized samples required that there be little or no enantiomeric enrichment during the crystallization, as was the case of the sulfone (+)-54.

The enantiomeric purity of the sulfide (+)-34, $[\alpha]_{436}^{RT}$ + 266° (c 0.656, CH_2Cl_2), obtained from the synthesis was therefore 86.0% based on the purity of its corresponding sulfone. Therefore, the absolute rotation of the sulfide 34 was calculated to be $[A]_{436}^{RT}$ 309° (c 0.656, CH_2Cl_2). Comparing the rotations of the sulfide, $[\alpha]_{436}^{RT}$ + 55.6° corr., derived from the Sommelet rearrangement with this absolute rotation, the optical purity of the product was 18.0%. In a similar correlation for the sulfone, $[\alpha]_{436}^{RT}$ + 31.6° (c 0.567, $CHCl_3$), derived from the Sommelet rearrangement, the optical purity of the product was 18.3%. These values of optical purity are in excellent agreement with the enantiomeric purity estimation obtained using the chiral shift reagent.

Preparation of Optically Active Methyl α-(2-methyl-5-chlorophenyl)ethyl Sulfide (41)

With the experience gained in preparing the active nitro-sulfide, experiments were initiated to prepare the active chloro-sulfide 41 in a similar manner. The critical stages in the nitro-system involved the isolation of the tosylate 81 and a successful resolution of the alcohol 51. The tosylate 81 had been so reactive under the experimental conditions that a high yield of the corresponding chloride accompanied the tosylate. Reaction of the chloro-alcohol 60 with brosyl chloride or tosyl chloride in a manner similar to that described for reaction of the nitro-alcohol 51 resulted only in the isolation of the corresponding chloride 82. No pyridinium hydrochloride could be precipitated from the reaction solution even with seeding. This result was not unexpected

in view of the substituent change from nitro to chloro resulting in a more stabilized benzyl carbonium ion from the reactive sulfonate ester of the chloro-system. Simultaneously with these experiments to prepare the sulfonate esters of 60, the resolution of the alcohol was attempted via its hydrogen phthalate 83. The preliminary results presented in the experimental section indicate that the optically pure alcohol 60 might be obtained via resolution of 83 with the α-phenylethyl amines.

The search for an alternate route to the active sulfide 41, which would not involve reactions at the reactive asymmetric center, resulted in the study of the resolution of α-(2-methyl-5-chlorophenyl)-ethanethiol ((±)-94). The thiol was readily available by reaction of the bromide 61 with sodium hydrogen sulfide. The techniques considered for this thiol were based on those routinely described in the standard reference books for the resolution of alcohols.

Consideration was given first to the diastereomeric salt method of resolution. For this purpose, the hydrogen thiolphthalate 85 was prepared by reaction of the thiol 84 with phthalic anhydride in pyridine. However, the attempts to resolve 85 by the salt method with either (-)-78 or brucine led to the complete destruction of the α-arylethyl moiety. In both instances, active solids could be precipitated, but these were shown by N.M.R. spectroscopy to lack the necessary functionality. The N.M.R. spectra of the evaporation residues of the mother liquors showed three principle singlets at δ 2.67, 2.22 and 1.28, all of which remain unassigned. Therefore, the salt method was abandoned in search of a method involving completely covalently bonded diastereoisomers.

After the consideration of many possible resolving agents that would give covalently bonded diastereoisomers with thiols, menthyl chloroformate (86) was selected as resolving agent. The successful chromatographic resolution of diastereomeric esters from the reaction of alcohols and amines with 86 has been reported by Westley and Halpern (84). Menthyl chloroformate was prepared according to the method of Einhorn and Rothlauf (85) from menthol and phosgene in a pyridine-benzene solvent mixture. The addition of 86 to an ethereal solution of sodium α-(2-methyl-5-chlorophenyl)ethanethiolate, prepared from sodium hydride and 84, resulted in the immediate precipitation of sodium chloride. After filtering the reaction mixture and concentration of the mother liquor, O-menthyl α-(2-methyl-5-chlorophenyl)ethyl thiolcarbonate (87), $[\alpha]^{RT}_{365}$ - 147° (c 1.0, benzene) was obtained as an oil.

Partial resolution of the thiolcarbonate was achieved by column chromatography of the oil on aluminum oxide (Woelm neutral, activity one) using sequentially the solvents Skellysolve B, benzene, and ether as eluants. Skellysolve B was used to elute the faster eluting fractions containing thiolcarbonate of rotation greater than $[\alpha]^{RT}_{365}$ - 150°. Intermediate fractions with rotations between $[\alpha]^{RT}_{365}$ - 50 and - 150° were collected with benzene and finally the column was flushed with ether to remove the slower eluting fractions. The quantities of the faster and slower eluting fractions were increased by recycling the intermediate fractions. Finally the extreme fractions were recycled on the column so as to increase their respective diastereomeric purities. In this manner, sizeable quantities of the faster eluting, $[\alpha]^{RT}_{365}$ ca. - 240°, and the slower eluting, $[\alpha]^{RT}_{365}$ ca. 0°, fractions

were obtained.

At this stage, it was desirable to know the extent of resolution. The diastereomeric purity of these fractions could not be determined by N.M.R. spectroscopy as their spectra were identical. A method of estimating the extent of the resolution from the optical yields of consecutive crops in a fractional crystallization of a solid derivative of the resolved thiol appeared most beneficial as the procedure would serve to improve the extent of the resolution as well. Therefore, the thiol (-)-84, $[\alpha]_{365}^{RT}$ - 61.7° (c 0.70, $CHCl_3$) was obtained from a methoxide catalyzed transesterification reaction of a quantity of the faster eluting thiolcarbonate, $[\alpha]_{365}^{RT}$ - 281° (c 2.13, benzene). Conversion of the active thiol to either its 3,5-dinitrothiolbenzoate 88 or p-nitrothiolbenzoate 89 gave solid esters. The fractional crystallization of these esters was inefficient leaving the slightly enriched ester in the mother liquor. From the optical yields, however, the thiol appeared to be 20 - 30% optically pure. The obtaining of optically pure thiol 84 from the combination of resolution via its diastereomeric thiolcarbonate and enantiomeric enrichment of its thiolbenzoate 88 or 89 seemed too laborious a procedure to warrant further work, although with suitable modifications, the procedure may have provided a general resolution technique worthy of consideration.

Attention was diverted to preparing derivatives of the sulfide 41 which might be suitable for deriving optically pure materials. As described in Chapter Three, oxidation of the sulfide with excess H_2O_2 in acetic acid gave directly the corresponding solid sulfone 62. This sulfone was therefore a candidate for the fractional crystallization

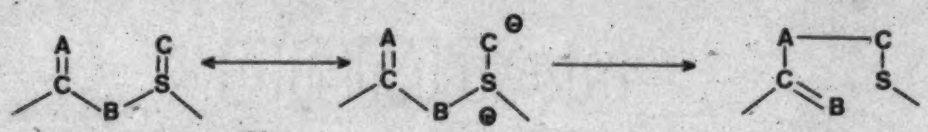
of the racemate from the active or *vice versa* such that optically pure material might be obtained easily. Therefore, active thiol (-)-84, $[\alpha]^{RT}_{365}$ - 51.5° (*c* 3.15, $CHCl_3$) was converted to its sulfide (-)-41, $[\alpha]^{RT}_{436}$ - 75.4°, $[\alpha]^{RT}_{365}$ - 122° (*c* 3.07, benzene) by the alkylation of its thiolate with methyl iodide. The sulfide was oxidized with excess H_2O_2 in acetic acid to give the crude sulfone (-)-62, $[\alpha]^{RT}_{365}$ - 31.3° (*c* 3.46, $CHCl_3$). Recrystallization of this material from chloroform-Skellysolve B solvent mixture gave the racemic sulfone, m.p. 143 - 144°. Concentration of the mother liquor yielded a crude evaporation residue, $[\alpha]^{RT}_{365}$ - 113° (*c* 0.851, $CHCl_3$). Recrystallization of this evaporation residue twice from benzene-Skellysolve B solvent mixture gave the sulfone (-)-62, m.p. 99 - 100°, $[\alpha]^{RT}_{365}$ - 127° (*c* 0.522, $CHCl_3$ or benzene), of constant optical rotation. In this instance, the differential in solubilities of the racemate and active sulfone was sufficient to make available the optically pure sulfone. This contrasted the attempts to enrich the thiolbenzoates in which a clean separation of isomers was not achieved.

The enantiomeric purity of the latter sulfone was confirmed to be 100% by observing spectral shifts for only one enantiomer in the N.M.R. spectrum of (-)-62 in the presence of $Eu(hfbc)_3$. Based on the observed absolute rotation of $[A]^{RT}_{365}$ 127° (*c* 0.52, benzene), the optical purity of the crude non-crystallized sulfone, $[\alpha]^{RT}_{365}$ + 26.9° (*c* 0.29, benzene), derived from the Sommelet rearrangement was 21.2%. The difference of *ca.* 4% between the optical purity estimation and that for enantiomeric purity is attributed to the small sample size of the crude non-crystallized sulfone and the

errors associated in determining its accurate weight. The absolute rotation of the sulfide 41 was estimated to be $[A]^{RT}_{365}$ 265° based on a correlation of the enantiomeric purity of 25.0% for a crude non-crystallized sample of sulfone obtained from oxidation of the sulfide (+)-41, $[\alpha]^{RT}_{365}$ + 66.2° (c 0.66, benzene).

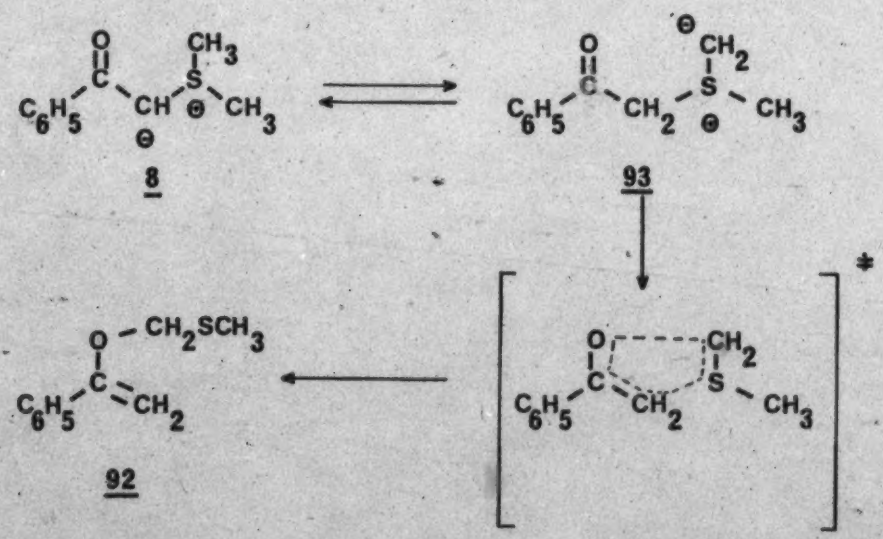
Discussion

The base-catalyzed rearrangement of sulfonium salts is representative of a general process of bond reorganization proceeding via sulfonium ylids and characterized by the conversion of 90 to 91. In the case of the Sommelet rearrangement, the participating double bond is embodied within an aromatic ring. The sulfonium ylids capable of this general reorganization have varying structural features and are generated under a variety of conditions as illustrated by the following examples.



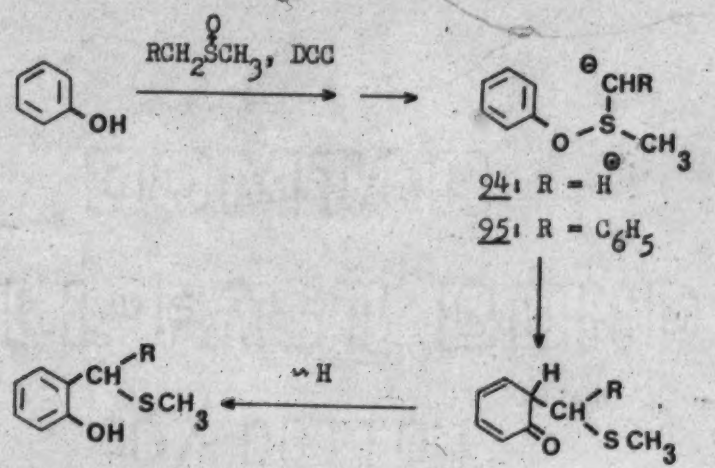
90 91

The rearrangement of dimethylsulfonium phenacylid (8) to α-(methylthio)methoxystyrene (92) in refluxing water was postulated by Ratts and Yao (86) to involve reversible ylid formation to the less stable methylid 93 in the protic solvent with rearrangement occuring via a cyclic transition state.

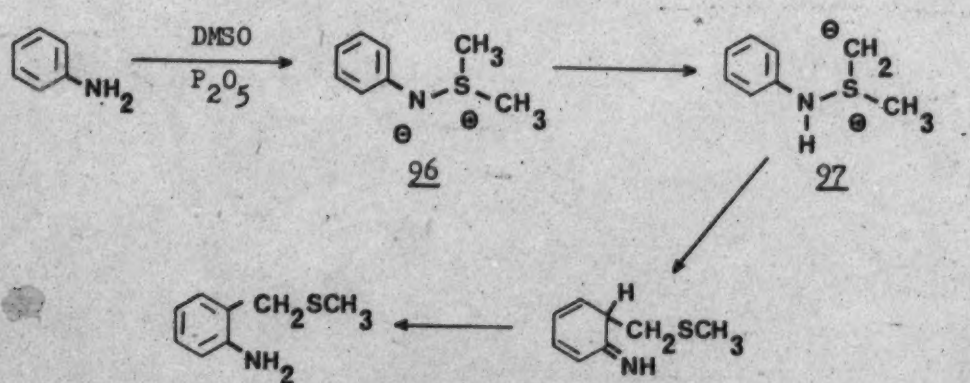


8 93 92

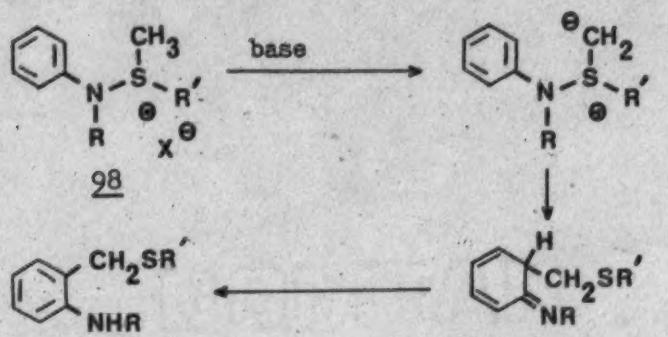
Phenols in the presence of dicyclohexyl carbodiimide and dimethyl sulfoxide undergo thiomethoxymethylation of the ortho position via the intermediacy of the ylid 94 (87). When the unsymmetrical benzyl methyl sulfoxide was used, ring alkylation occurred to give the more highly substituted product from the more stabilized benzylid 95 than to give product from the corresponding methylid.



An analagous thiomethoxymethylation of aromatic amines has been reported by Claus and Vycudilik (88) to occur via the intermediacy of the sulfimide 96 and sulfonium ylid 97.

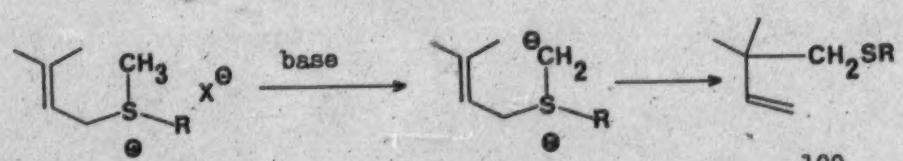


P. Gassman and co-workers (89) and C. R. Johnson and co-workers (90) in communications published simultaneously reported the ortho alkylation rearrangement for several aminosulfonium salts (also named azasulfonium salts) 98 upon base treatment.



98

Baldwin and co-workers in a series of communications (91) have described the allyl rearrangement of several allyl sulfonium salts upon base treatment, for example the conversion of 99 to 100.

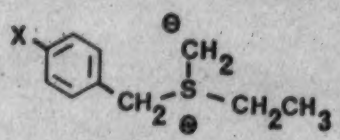


99 100

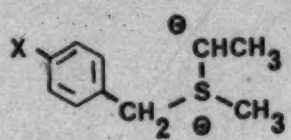
Consideration of the principles of conservation of orbital symmetry (92) suggested this reaction to be a symmetry-allowed [2,3] sigmatropic rearrangement (91,93). A sigmatropic change of order [i,j] is defined as the migration of a σ-bond, flanked by one or more π electron systems, to a new position whose termini are i - 1 and j - 1 atoms removed from the original bonded loci, in an uncatalyzed intramolecular process. It was implied that the generalized process 90 → 91 for all sulfonium ylids could be considered as concerted [2,3] sigmatropic

rearrangements, including the Sommelet rearrangement.

On the basis of the relative acidities (94) of α-protons of ethyl and methyl substituents in sulfonium salts, it is expected that the methylid 101 would be formed in a greater concentration than the corresponding ethylid 102 in the equilibrium solution. That proton abstraction was not product determining was evidenced by the product balance favouring rearrangement from the more highly substituted ylid 102.

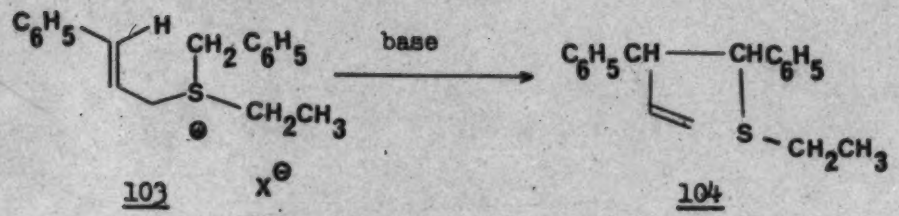


101

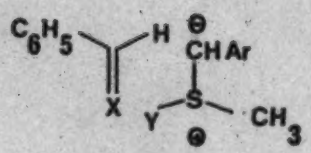


102

Ollis, et al suggested there was a diastereotopic selectivity of proton abstraction upon ylid formation during the allyl rearrangement 103 → 104 on the basis of the 40/60 mixture of two diastereomeric racemates isolated (93). However, this non-equal mixture of diastereoisomers could have arisen from a selective reactivity of one of the stereoheterotopic faces of the terminal carbon of the allylic group with the benzylid. That there may have been little diastereotopic selectivity upon ylid formation to provide a pyramidally stable carbanion is implied by the observation of low optical yields in the oxirane 28 from the reaction of the benzylid 22 with benzaldehyde and in the oxirane synthesis from the ylid from the chiral sulfonium salt 67c as described by Darwish and Nakamura (64). The similarity between the oxirane synthesis and the allyl rearrangement is seen in that both involve potential induction of asymmetry upon benzylid formation and reaction of the benzylid with an electrophilic double bond, see 105.

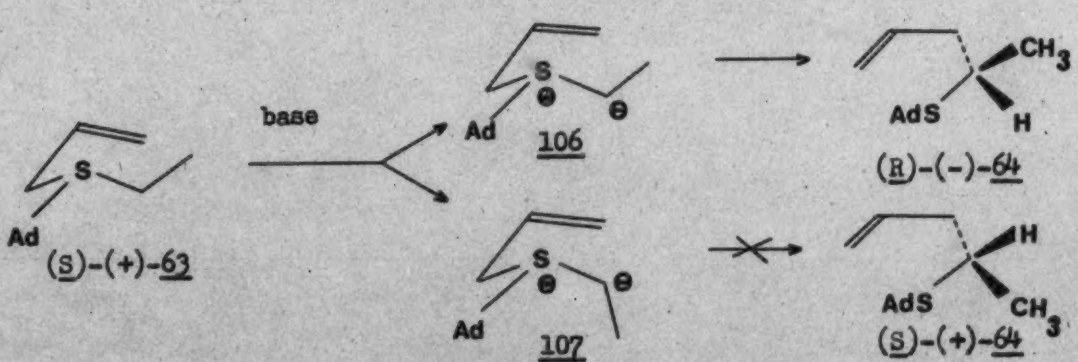


103 $X^{\ominus}$ 104

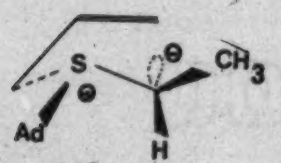


105

The efficient transfer of asymmetry (<94%) from sulfur to carbon in the allyl rearrangement of (+)-adamantylallylethylsulfonium tetrafluoroborate ((+)-63), taken as further evidence of the concertedness of the allyl rearrangement, was depicted by Trost and Hammen to proceed from the ylid 106 as the non-bonded interactions of this conformer would be minimized compared with those of 107 (62). This representation of the ylid 106, which fails to adequately describe the geometry of the carbanion, suggests that the asymmetric transfer is due to stereochemical control in the cyclic transition state. Unfortunately, it was not stated whether the possibility



that the transfer resulted from a diastereotopic selectivity of proton abstraction giving the pyramidal carbanion depicted as 108 was considered. If, however, pyramidal inversion of this α-carbanion is much more rapid than rearrangement, clearly, the kinetic average of the invertomers of the carbanion, depicted as 109, will experience fewer non-bonded interactions than the conformations resulting from a 180° rotation of the C—S bond.



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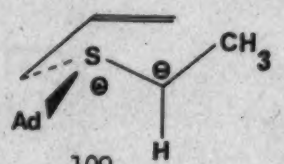
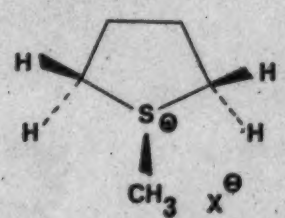


109

Fava, et al have observed a case of diastereotopic selectivity of proton abstraction in the deuterium - hydrogen exchange reaction on 110 in basic D_2O, for which the protons cis to the S-methyl group exchanged considerably faster than the protons trans (94,95). Although this result agrees with that predicted by the Gauche Effect, it should not now be considered substantiating evidence of the theory in the



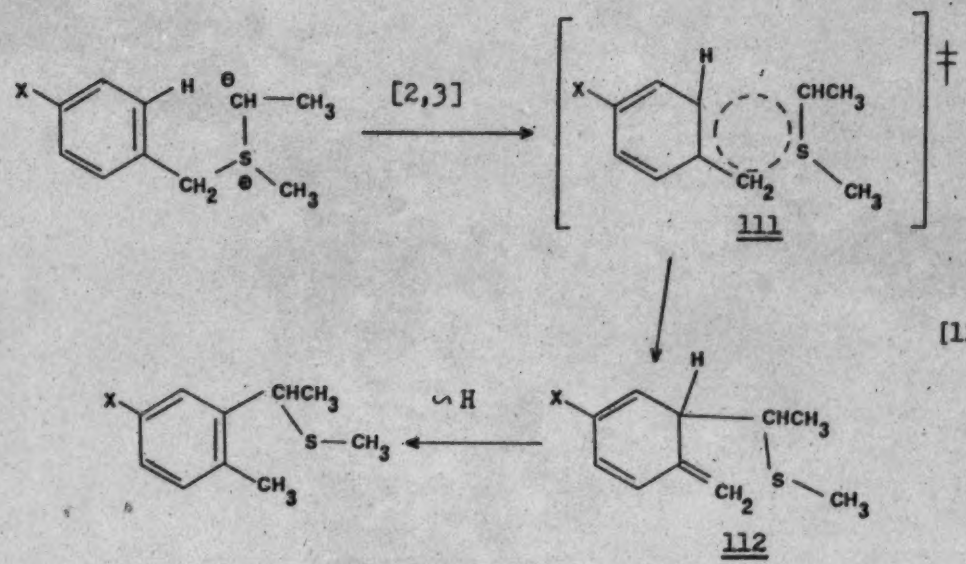
110

light of the discrepencies in the predictability of the theory with several observations as outlined previously in Chapter Three. In any event, this demonstration of diastereotopic selectivity of proton abstraction adjacent to a pyramidal sulfonium atom to produce a pyramidally stable carbanion cannot be considered a general case until the conformational effect of the ring system have been removed from the reaction. The oxirane synthesis with the ylids of the optically active salts 21 and 67c tested the possibility of an induction of asymmetry at the α-carbon in a system free of the conformational constraints of a ring system. The negligible optical yields of the oxiranes suggest that either a diastereotopic selectivity of proton removal is unimportant or that the carbanion cannot maintain its stereochemistry prior to acting as a nucleophile. However, in terms of the allyl and Sommelet rearrangements, stereochemical control in the transition state appears more important.

The allyl and Sommelet rearrangements are examples of self-immolative transformations in which the inducing chiral center is destroyed at the same time that a new chiral center is created. The lower efficiency of asymmetric transfer in the Sommelet rearrangements, 20 - 25% compared with <94% for the allyl rearrangement, was anticipated because of the greater opportunity for the racemization of the inducing sulfonium center under the reaction conditions. The temperatures of the Sommelet rearrangements , 25° and 70°, were significantly higher than that necessary for the allyl rearrangement, - 33°. The much higher temperatures of the Sommelet rearrangements were of course necessary to compensate for the loss of resonance stabilization in the aromatic ring in proceeding from the ylid.

At these higher temperatures, the stereochemical integrity of the asymmetric sulfur will have been reduced due to pyramidal inversion. The rate constants for the loss of optical activity for (+)-21 in methanol at 70° was found to be $(9.15 \pm 0.13) \times 10^{-5}$ seconds^{-1} (36) and for (+)-35 in methanol at 50 and 70° were $(6.60 \pm 0.09) \times 10^{-6}$ seconds^{-1} and $(9.66 \pm 0.06) \times 10^{-5}$ seconds^{-1} respectively (44). At 70°, in the time necessary to accomplish the Sommelet rearrangement of 35, the salt would have undergone one half-life of racemization ($t_{\frac{1}{2}}$ ca. 2 hours) in the absence of methoxide ion. If the ylids derived from this salt recemized at even faster rates than the salt, as was found for ethylmethylsulfonium phenacylid ((-)-5) which racemized 200 times faster than its salt (9), then a further loss of the stereochemical integrity of the sulfonium center would have resulted. The pyramidal sulfur of (+)-63 would not be expected to racemize to any significant extent during the one hour reaction at - 33°. A considerable portion of the loss of stereospecificity in the asymmetric synthesis of the Sommelet sulfides was therefore due to racemization via pyramidal inversion of the chiral sulfonium center.

A detailed examination of the intermediate stages of the Sommelet rearrangement of (R)-(+)-35 has permitted an assignment of absolute configuration to the sulfide (+)-41 obtained. Eq. [12] outlines the proposed mechanism for the rearrangement from the S-ethyl substituent proceeding via the cyclic transition state 111. This rearrangement differs from the allyl rearrangement of (+)-63 in that the initial product consists of a set of diastereomeric sulfides 112 rather than a set of enantiomers. However, under the reaction conditions



[12]

the set of diastereomeric sulfides was reduced to a set of enantiomers upon re-aromatization.

Projections of the four reactive conformations of the ylid from (R)-(+)-35 expected to lead to the set of diastereoisomeric sulfides 112 are illustrated in Figure XVI. Conformations 113 and 114 involve the attack of the re face of the kinetic average of a planar carbanion upon the re face and si face of an ortho carbon of the aryl moiety respectively. Conformations 115 and 116 involve the attack of the si face of the carbanion upon the si and re face of an ortho carbon respectively. It should be noted that the viewing from one side of a substituted ring can provide two ortho carbons with different stereohetereotopic faces. The conformations 113 and 114 are obtained simply by rotation of the sulfur-benzylic carbon bond and not by a 180° rotation of the aryl-benzylic carbon bond. The latter rotation would interchange the carbons to be viewed but would not change the designation of the face of the ortho carbon viewed or the configuration of a product from attack at that face. More severe non-bonded

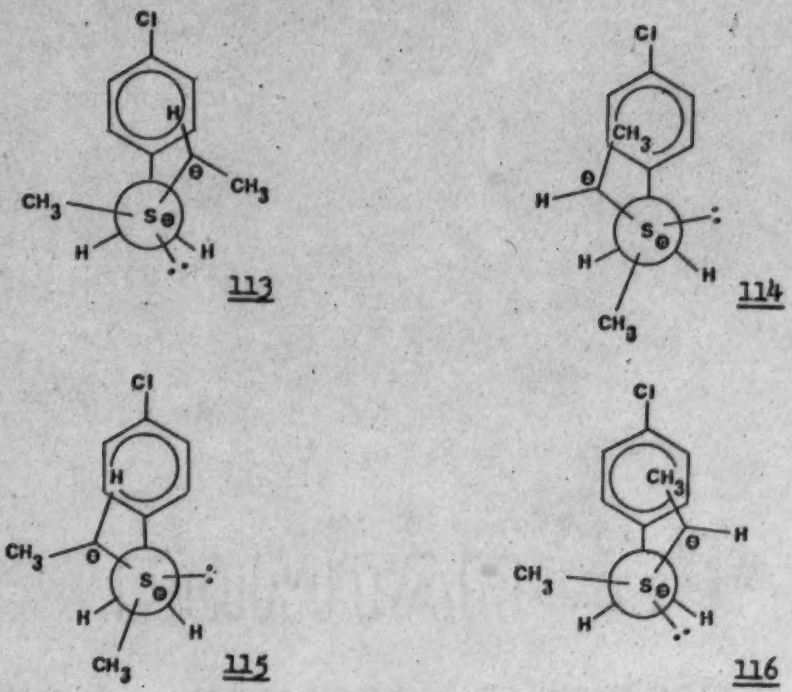


Figure XVI. Projections of the four reactive conformations of the ylid from (R)-(+)-35.

interactions between the aromatic ring and the methyl substituent of the carbanion would tend to disfavour the conformations 114 and 116 over 113 and 115. In the 5-membered cyclic transition states leading from 113 - 116, extensive eclipsing of substituents occurs as illustrated by the Newman projections of the developing C—C bond and of the ylid bond, Figure XVII. It is seen that the more favourable conformations 113 and 115 lead to transition states in which the substituents about the developing C—C are partially eclipsed whereas the less favourable conformations 114 and 116 give transition states where the substituents are fully eclipsed. Consideration of the eclipsing about the ylid bond provides the key

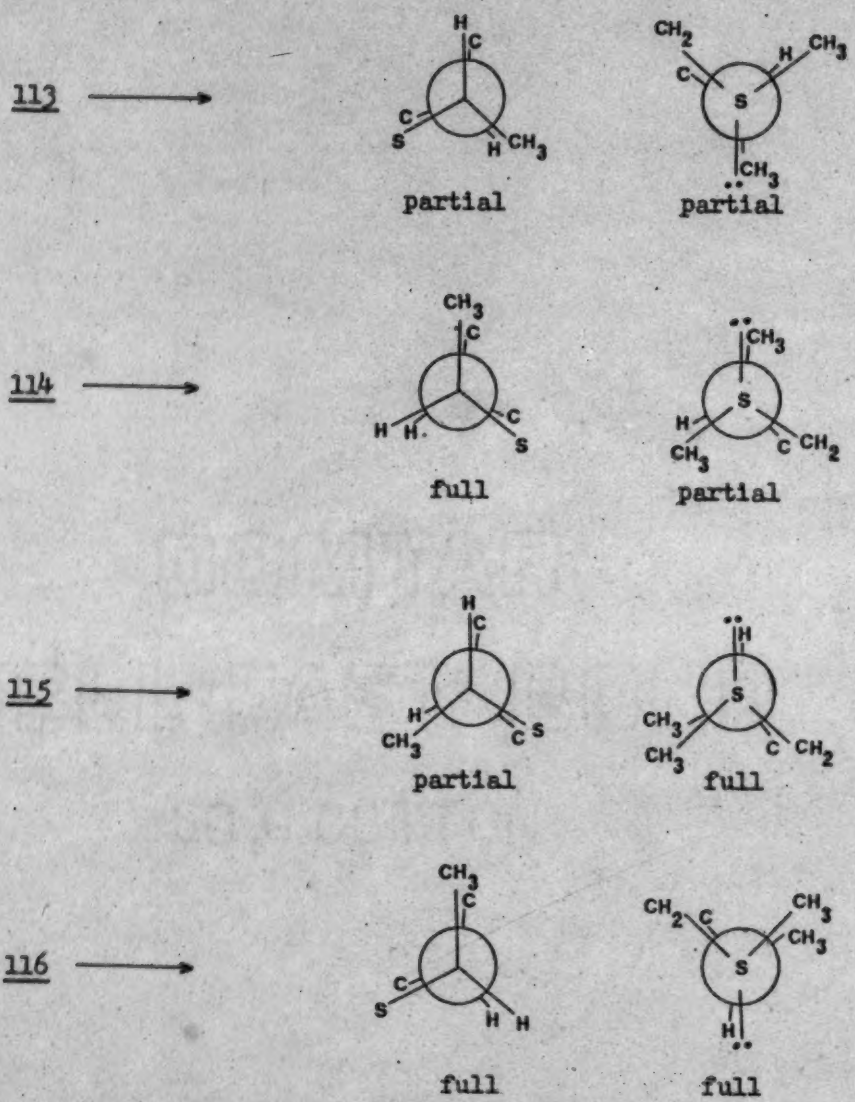
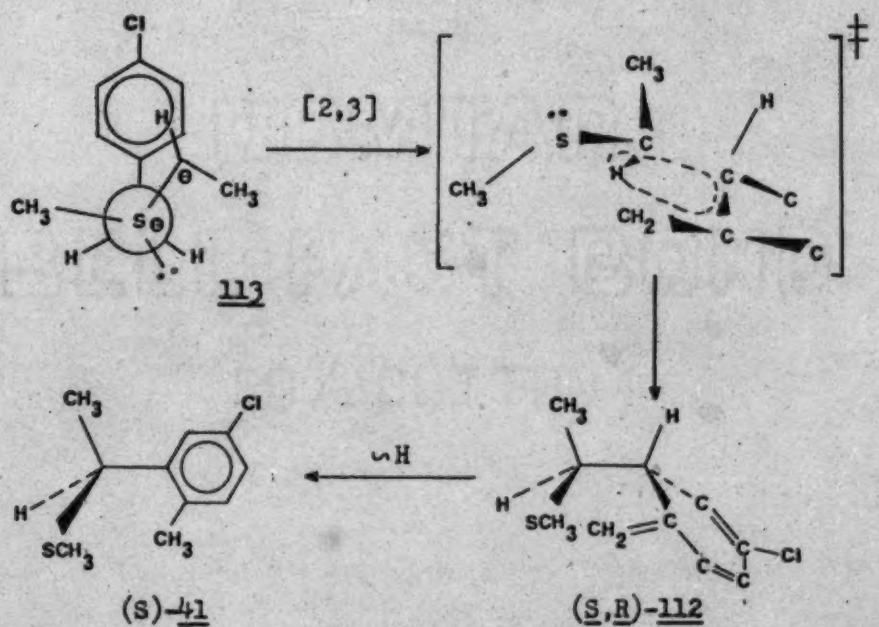


Figure XVII. Newman projections of the developing C—O bond and the ylid bond in the cyclic transition states from 113 - 116.

determinant for the assignment of configuration to the sulfide eventually produced. For the cyclic transition state from the conformation 113, the substituents about the ylid bond are partially eclipsed whereas those from the cyclic transition state from 115 are fully eclipsed. Therefore rearrangement is expected to proceed preferentially from 113.

Prefered rearrangement from the reactive conformation 113 would provide the (S,R)-diastereoisomer of 112 whereas rearrangement from 115 would provide the (R,S)-diastereoisomer of 112. These latter two isomers of 112 are enantiomers which are clearly derived from diastereomeric transition states. Re-aromatization of (S,R)-112 destroys the R center and provides sulfide of the S configuration. Therefore, (+)-41 is assigned the S configuration.



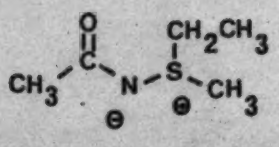
113

(S)-41 (S,R)-112

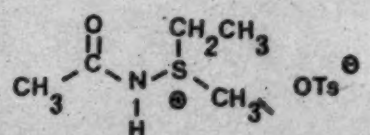
This assignment of S configuration to (+)-41 permits similar assignments to be made for the corresponding thiol (+)-84 and the sulfone (+)-62, as these compounds were interrelated in reactions not affecting the chiral center. It can also be concluded that the R enantiomer of the sulfone 62 is shifted further downfield in the N.M.R. spectra of the sulfone in the presence of $Eu(hfbc)_3$. The similarity of the lanthanide induced shifts for (+)-54 and (+)-62 suggests that a similar assignment of configuration may be extended

to the entire nitro-series of compounds prepared with a (+) sign of rotation excepting the salt (+)-21 which would have R configuration in accord with the mechanism proposed for the Sommelet rearrangement of (R)-(+)-35.

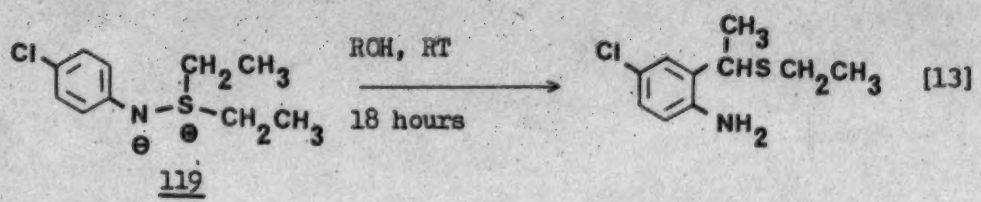
The observation of asymmetric synthesis in the allyl and Sommelet rearrangements suggests that similar observations might be observed in other systems of the generalized process 90 → 91. For example, a more efficient transfer of asymmetry in an ortho alkylation reaction than that for the Sommelet rearrangement is predicted on the basis of the following recent reports in the literature. Menon and Darwish (96) have found the chiral sulfonium ylid, N-acetylethylmethylsulfimide 117 to racemize 1/46 as fast as its corresponding aminosulfonium salt 118 which racemizes with $k_{rac} = 1.65 \times 10^{-6}$ seconds^{-1} at 70° in acetonitrile. Claus and co-workers have recently found the achiral N-p-chlorophenyldiethylsulfimide (119) to undergo the ortho alkylation rearrangement depicted in eq. [13] (97). Therefore, the unknown ylid, N-p-chlorophenylethylmethylsulfimide should serve as a suitable substrate for an asymmetric systhesis of an aromatic amine. The extent of asymmetric transfer is expected to be higher than those observed for the Sommelet rearrangements because the sulfimide is expected to maintain its stereochemical integrity better than the ylids derived from the benzylsulfonium salts.



117



118



119 [13]

Experimental

Anhydrous Pyridine

Anhydrous pyridine was prepared by distillation from barium oxide with the careful exclusion of moisture and storage of the center-cut of the distillate over KOH pellets (26).

Tris[3-(heptafluorobutyryl)-d-camphorato]-europium(III) ($Eu(hfbc)_3$)

$Eu(hfbc)_3$ was obtained from Willow Brook Laboratories, Inc. under the trade name Eu Optishift II. It was stored in a desicator and used without purification.

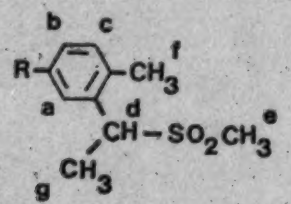
Effect of $Eu(hfbc)_3$ on the N.M.R. Spectra of Sulfones

A Varian HA 100 Analytical Spectrometer was used for the enantiomeric purity analyses of the sulfones. Typically a stock solution of the shift reagent was prepared by dissolving ca. 60 mg $Eu(hfbc)_3$ in 0.3 ml. $CDCl_3$. Using a fine-tipped disposable pipette, the stock solution was added dropwise to a solution of the sulfone in a N.M.R. tube. The tube was capped and shaken to ensure adequate mixing of the solution. After recording the spectrum and having obtained the desired spectral shifts, the total drop count (ca. 50) of the stock solution was obtained and the final concentrations of the shift reagent and sulfone in the N.M.R. solution calculated. The full spectra were recorded first at a 1000 Hz. sweep width. The relative areas of the resonances being studied were determined from a series of six integrations at expanded sweep widths of 50 or 100 Hz. Per cent enantiomeric purity was calculated from the ratio of the difference of the integrations of enantiotopic protons to the sum of their integrations. The error was calculated as the average deviation from the mean of the six determinations.

Tables XIV and XV summarize the Lanthanide Induced Shifts (LIS) in the N.M.R. spectra of racemic samples of the sulfones 54 and 62 in the presence of added $Eu(hfbc)_3$. The differential shifts ($\Delta\delta$) between resonances of enantiotopic protons and the relative abundance of the enantiomer shifted further downfield to the whole enantiomeric mixture are also shown. The effect of added $Eu(hfbc)_3$ on the spectral shifts of the sulfones 45 and 58 are summarized in Table XVI and Table XVII respectively.

TABLE XIV

EFFECT OF ADDED Eu(hfbc)$_3$ ON THE N.M.R. SPECTRUM OF (±)-METHYL α-(2-METHYL-5-NITROPHENYL)ETHYL SULFONE (54) IN $CDCl_3$[a]



R = NO_2

Proton	LIS, ppm	Δδ, ppm
a	0.62	0.13
b	0.12	0.02
c	0.10	0.00
d	1.01	0.12
e	0.73	0.12
f	0.17	0.12
g	0.60	0.13

CALIBRATION OF ENANTIOMERIC PURITY ESTIMATION OF (±)-54[b] USING THE PEAK AREAS OF THE S-METHYL RESONANCES (e and e')[c]

Integration	Proton e	Proton e'	Total Integ.	% Ratio e/e+e'
1	11.29	11.45	22.74	49.6
2	10.72	11.13	21.84	49.1
3	10.48	11.30	21.78	48.1
4	10.56	11.08	21.64	48.8
5	10.60	11.32	21.92	48.4
6	10.58	11.10	21.68	48.8

Average ± average deviation = 48.8 ± 0.4%

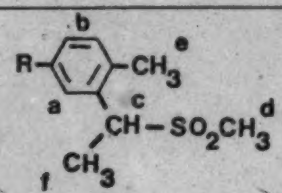
a: 0.034 M Eu(hfbc)3; 0.25 M sulfone 54; molar ratio 0.14.

b: Sweep offset 330 Hz.; sweep time 100 sec.; sweep width 50 Hz.

c: Singlets at δ 3.62 and 3.51; band widths of 10 Hz.

TABLE XV

EFFECT OF ADDED $Eu(hfbc)_3$ ON THE N.M.R. SPECTRUM OF (±)-METHYL α-(2-METHYL-5-CHLOROPHENYL)ETHYL SULFONE (62) IN $CDCl_3$[a]



R = Cl

proton	LIS, ppm	Δδ, ppm
a	0.71	0.14
b	0.09	0.00
c	1.13	0.12
d	0.76	0.09
e	0.20	0.02
f	0.71	0.15

CALIBRATION OF ENANTIOMERIC PURITY ESTIMATION OF (±)-62[b] USING THE PEAK AREAS OF THE S-METHYL RESONANCES (d and d')[c]

Integration	Proton d	Proton d'	Total Integ.	% Ratio d/d+d'
1	11.23	11.16	22.39	50.2
2	11.04	11.30	22.34	49.4
3	10.55	10.90	21.45	49.2
4	10.90	11.21	22.11	49.3
5	11.36	11.14	22.50	50.5
6	10.95	11.07	22.02	49.7

Average ± average deviation [illegible].7 ± 0.4%

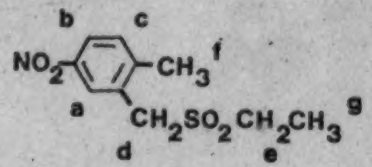
a: 0.057 M $Eu(hfbc)_3$; 0.17 M sulfone 62; molar ratio 0.34.

b: Sweep offset 325 Hz.; sweep time 100 sec.; sweep width 50 Hz.

c: Singlets at δ 3.64 and 3.56; band widths of 8 Hz.

TABLE XVI

EFFECT OF ADDED $Eu(hfbc)_3$ ON THE N.M.R. SPECTRUM OF ETHYL 2-METHYL-5-NITROBENZYL SULFONE (45) IN $CDCl_3$[a]

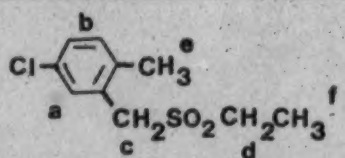


Proton	LIS, ppm	Δδ, ppm
a	0.70	0
b	0.18	0
c	0.20	0
d	2.37	0.02
e	2.52	0.02
f	0.42	0
g	0.90	0

a: 0.039 M $Eu(hfbc)_3$; 0.11 M sulfone 54; molar ratio 0.35.

TABLE XVII

EFFECT OF ADDED $Eu(hfbc)_3$ ON THE N.M.R. SPECTRUM OF ETHYL 2-METHYL-5-CHLOROBENZYL SULFONE (58) IN $CDCl_3$[a]



Proton	LIS, ppm	Δδ, ppm
a	1.09	0
b	0.28	0
c	2.59	0.05
d	2.41	0.05
e	0.71	0
f	1.42	0

a: 0.039 M $Eu(hfbc)_3$; 0.11 M sulfone 58; molar ratio 0.35.

Enantiomeric Purity Measurements

The enantiomeric purity of the optically active sulfone 54, $[\alpha]^{RT}_{436}$ + 31.6° (c 0.567, $CHCl_3$), derived from the sulfide (+)-34 isolated from the products of the nitro-Sommelet rearrangement as described in Chapter Three, was determined as summarized in Table XVIII. In addition, a 50 ml. aliquot of the decomposition solution from the rearrangement was concentrated and the evaporation residue oxidized with 0.171 g (1.50 mmole) 30% H_2O_2 in 3 ml. acetic acid at 100° for three hours. The crude oxidized product isolated in a manner similar to that described for the isolation of the pure racemic sulfone was titurated in 0.4 ml. $CDCl_3$ and filtered into an N.M.R. tube. The solution was titrated with a stock solution of $Eu(hfbc)_3$ until the desired N.M.R. spectral shifts for the active sulfone were observed. The enantiomeric purity of the sulfone in the crude product was determined as summarized in Table XVIII. The resonances due to the other compounds did not interfer with the analysis as the region studied was free of extraneous signals.

The enantiomeric purity of the optically active sulfone 62, $[\alpha]^{RT}_{365}$ + 26.9° (c 0.29, benzene), derived from the sulfide 41 isolated from the products of the chloro-Sommelet rearrangement as described in Chapter Three, was determined as summarized in Table XIX. In this experiment involving the sulfone 62, too much stock solution of the shift reagent was added such that the downfield S-methyl resonances were overlapping with the resonance at δ 4.88 due to the shift reagent. Therefore, the α-methyl doublet resonances were used, only in this instance, to determine the enantiomeric purity of the sulfone.

TABLE XVIII

ESTIMATION OF ENANTIOMERIC PURITY USING THE N.M.R. PEAK AREAS OF THE SULFONE (+)-54 DERIVED FROM THE NITRO-SOMMELET REARRANGEMENT

A - for the isolated sulfone[a]

Integration[b]	Proton e[c]	Proton e'	Total Integ.	Difference	% E.P.
1	9.23	13.72	22.95	4.49	19.6
2	9.56	13.80	23.36	4.24	18.2
3	8.92	13.58	22.50	4.66	20.7
4	9.23	13.60	22.83	4.37	19.1
5	9.28	13.50	22.78	4.22	18.5
6	9.25	14.05	23.30	4.80	20.6

Average ± average deviation = 19.5 ± 0.7%

B - for the crude oxidized product[d]

Integration[e]	Proton e[f]	Proton e'	Total Integ.	Difference	% E.P.
1	9.04	13.72	22.76	4.68	20.6
2	9.10	13.47	22.57	4.37	19.4
3	9.10	13.58	22.68	4.48	19.8
4	9.00	13.75	22.75	4.75	20.9
5	9.07	13.59	22.66	4.52	19.9
6	8.95	13.78	22.73	4.83	21.3

Average ± average deviation = 20.3 ± 0.7%

a: In $CDCl_3$; 0.034 M $Eu(hfbc)_3$; 0.25 M sulfone 54; ratio 0.14.

b: Sweep offset 330 Hz.; sweep time 100 sec.; sweep width 50 Hz.

c: S-methyl singlets at δ 3.64 and 3.52; band widths of 8 and 9 Hz. respectively.

d: In $CDCl_3$; 0.07 M $Eu(hfbc)_3$; ca. 0.23 M sulfone 54; ca. 0.08 M sulfone 45.

e: Sweep offset 330 Hz.; sweep time 100 sec.; sweep width 50 Hz.

f: S-methyl singlets at δ 3.65 and 3.56; band widths of 8 and 9 Hz. respectively.

TABLE XIX

ESTIMATION OF ENANTIOMERIC PURITY USING THE N.M.R. PEAK AREAS OF THE SULFONE (+)-62 DERIVED FROM THE CHLORO-SOMMELET REARRANGEMENT

A - for the isolated sulfone[a]

Integration[b]	Proton f[c]	Proton f'	Total Integ.	Difference	% E.P.
1	8.13	14.29	22 42	6.16	27.5
2	8.52	14.23	22.75	5.71	25.1
3	8.06	14.13	22.19	6.07	27.4
4	8.52	14.26	22.78	6.74	25.2
5	7.80	14.13	21.93	6.33	28.9
6	7.84	13.90	21.74	6.06	27.9

Average ± average deviation = 27.0 ± 1.2%

B - for the crude oxidized product[d]

Integration[e]	Proton d[f]	Proton d'	Total Integ.	Difference	% E.P.
1	8.34	14.12	22.46	5.78	25.7
2	8.29	14.00	22.29	5.71	25.6
3	8.50	14.35	22.85	5.85	25.6
4	8.40	14.00	22.40	5.60	25.0
5	8.30	14.20	22.50	5.90	26.2
6	8.44	14.00	22.44	5.56	24.8

Average ± average deviation = 25.5 ± 0.4%

a: In $CDCl_3$; 0.064 M $Eu(hfbc)_3$; ca. 0.15 M sulfone 62; ratio 0.43.

b: Sweep offset 310 Hz.; sweep time 250 sec.; sweep width 50 Hz.

c: α-Methyl doublets at δ 3.58 and 3.25; band widths of 15 Hz.

d: In $CDCl_3$; 0.065 M $Eu(hfbc)_3$; ca. 0.17 M sulfone 62; ca. 0.05 M sulfone 58.

e: Sweep offset 390 Hz.; sweep time 250 sec.; sweep width 50 Hz.

f: S- methyl singlets at δ 4.34 and 4.18; band widths of 9 and 11 Hz. respectively.

The corresponding crude oxidized product was obtained by the oxidation of the evaporation residue obtained from a 5 ml. aliquot of the solution of products from the chloro-Sommelet rearrangement as described in Chapter Three with 0.115 g (1.0 mmole) 30% H_2O_2 in 3 ml. acetic acid at 100° for three hours. The enantiomeric purity of the sulfone 62 in the crude oxidized product was determined as summarized in Table XIX.

3β-Acetoxy-Δ^5-etienic Acid (72)

3β-Acetoxy-Δ^5-etienic acid was prepared following a procedure similar to that reported by Staunton and Eisenbraun (78). To a solution of 21 g (0.525 mole) sodium hydroxide in 180 ml. water at - 5°, was slowly added 21.5 g (0.134 mole) bromine. After the addition was complete, the solution was diluted with 120 ml. dioxane and maintained at 0°. The cold hypobromite solution was added to a solution of 14.8 g (0.04 mole) pregnenolone acetate (73) in 550 ml. dioxane and 160 ml. water while maintaining the temperature below 10°. After addition was complete, the mixture was stirred for two hours then quenched with a solution of 5 g anhydrous sodium sulfite in 50 ml. water. The reaction mixture was refluxed for 15 minutes and the clear solution, while still hot, acidified by the cautious addition of 25 ml. concentrated HCl. This mixture was cooled at 5° overnight. The precipitated 3β-hydroxy-Δ^5-etienic acid was filtered, dried, then titurated in 100 ml. dry pyridine at 90°. The hot solution was filtered and the mother liquor cooled and treated with 10 ml. acetic anhydride. After 18 hours, the excess of acetic anhydride

and the mixed anhydride in the reaction solution were hydrolyzed by the addition of 20 ml. water and the boiling of the resulting mixture until the precipitate had just dissolved. The clear solution was then diluted with 70 ml. water and cooled to precipitate the crude 3β-acetoxy-Δ^5-etienic acid, m.p. 225°. Crystallization of this material at room temperature from warm acetic acid yielded 4.13 g (0.0115 mole, 28.8%) 72; m.p. 238 - 240°; $[\alpha]^{RT}_{589}$ - 31.3° (c 1.35, $CHCl_3$) (reported $[\alpha]^{RT}_{589}$ - 32° ($CHCl_3$) (98)); N.M.R. ($CDCl_3$), δ 10.04 (s, 1H), 5.40 (m, 1H), 4.60 (broad, 1H), 2.04 (s, 3H), 1.04 (s, 3H), 0.76 (s, 3H); Infrared ($CHCl_3$), 3500 (w), 3000 (broad), 1700 (s), 1370 (m), 1360 (m), 1120 (w) cm^{-1}. Crystallization of the crude from chloroform-Skellysolve B or benzene-Skellysolve B solvent mixtures failed to give pure materials of constant specific rotation.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.41, 73.17; H, 8.78, 9.23.

α-(2-methyl-5-nitrophenyl)ethyl 3β-acetoxy-Δ^5-etienate (76)

Following the procedure of Steiger and Reichstein (79), a 0.500 g (1.39 mmole) quantity of 72 was treated with 1.75 ml. thionyl chloride for 4 hours at room temperature. Excess solvent was removed under reduced pressure to give the crude 3β-acetoxy-Δ^5-etienyl chloride (74). The alcohol 51 (0.258 g, 1.47 mmole) in 10 ml. pyridine was added to the crude chloride and the solution stirred for two days. The reaction mixture was poured into dilute HCl to precipitate the crude ester. The dried crude was titurated in 5 ml. benzene and the mixture filtered to yield 0.0631 g (0.09 mmole) 3β-acetoxy-Δ^5-etienic

anhydride (75) (79). The evaporation residue from the mother liquor was crystallized from benzene-Skellysolve B solvent mixture to yield 0.540 g (1.03 mmole, 70.2%) 76: m.p. 117 - 118°; $[\alpha]_{589}^{RT}$ - 20.3° (c 0.997, CH_2Cl_2); N.M.R. ($CDCl_3$), δ 8.30 (d, J = 2.4 cps, 0.5H) 8.25 (d, J = 2.4 cps, 0.5H), 8.01 (q, 1H), 7.30 (s, J = 8.4 cps, 1H), 6.09 (q, J = 6.5 cps, 1H), 5.40 (s, 1H), 4.58 (broad, 1H), 2.50 (s, 3H), 2.02 (s, 3H), 1.54 (d, J = 6.5 cps, 3H), 1.03 (s, 1.5H), 0.99 (s, 1.5H), 0.72 (s, 1.5H), 0.53 (s, 1.5H); Infrared ($CDCl_3$), 1715 (s), 1605 (w), 1445 (m), 1345 (s), 1075 (m), 1060 (s) cm^{-1}; Mass Spectra, m/e 463 (base), 448, 299, 285, 253, 191, 179, 164, 523 (parent, absent). Recrystallization of 76 from benzene-Skellysolve B solvent mixture failed to change its specific rotation or its N.M.R. spectrum.

Resolution of (±)-α-Phenylethyl amine ((±)-78)

α-Phenylethyl amine was resolved according to the procedure of Theilacker and Winkler (80). To 31.3 g d-tartaric acid dissolved in 450 ml. hot methanol was added 25 g (±)-78. The reaction mixture was cooled at 5° overnight to precipitate material with m.p. 176°. This precipitate was twice recrystallized from minimum amounts of hot methanol cooled to room temperature to give the less soluble diastereoisomer, m.p. 197 - 198°, $[\alpha]_{436}^{RT}$ + 19.2° (c 0.4, methanol). This salt was decomposed in 50 ml. 10% sodium hydroxide to liberate the amine which was extracted with ether. The extracts were washed with water, dried and concentrated. The residue was distilled under reduced pressure to yield (-)-α-phenylethyl amine ((-)-78): b.p. 76° (12 mm), α_{589}^{22} - 38.55°, $[\alpha]_{589}^{22}$ - 40.58° (neat) (reported $[\alpha]_{589}^{22}$ - 40.3° (neat), d_4^{22} = 0.95 (80)).

The original mother liquor of this resolution was concentrated and the optically impure amine isolated from the salt. Crude (+)-78, $[\alpha]^{RT}_{589}$ + 16.8° (c 2.4, $CHCl_3$) (14.5 g, 0.120 mole), was dissolved in 100 ml. 95% ethanol and the solution heated to reflux. Sufficient sulfuric acid in ethanol to neutralize the excess of the active over the racemic amine, 5.2 g concentrated sulfuric acid (0.0506 mole) in 150 ml. 95% ethanol, was added to the amine solution and the mixture cooled to room temperature. The precipitated hydrogen sulfate, m.p. 265 - 268°, $[\alpha]^{RT}_{365}$ + 18.5° (c 1.10, methanol) was isolated and decomposed in dilute sodium hydroxide liberating the amine which was recovered as described above for the (-)-isomer to give (+)-78, α^{22}_{589} + 38.41° (neat), $[\alpha]^{22}_{589}$ + 40.43° (neat).

α-(2-Methyl-5-nitrophenyl)ethyl Hydrogen Phthalate ((±)-77)

A 0.535 g quantity (2.96 mmole) of 51 and 0.437 g (2.96 mmole) phthalic anhydride were dissolved in 5 ml. dry pyridine and the solution heated on a steam bath for one hour. The reaction solution was cooled, diluted with 5 ml. acetone and neutralized with cold concentrated HCl. Addition of water precipitated the crude hydrogen phthalate. The precipitate was isolated and recrystallized from chloroform-Skellysolve B to yield 0.777 g (2.36 mmole, 79.7%) (±)-77; m.p. 145 ; N.M.R. ($CDCl_3$), δ 11.87 (s, 1H), 8.32 (d, J = 2.0 cps, 1H), 8.15 - 7.50 (m, 5H), 7.30 (d, J = 8.4 cps, 1H), 6.36 (q, J = 6.5 cps, 1H), 2.55 (s, 3H), 1.66 (d, J = 6.5 cps, 3H); Infrared ($CDCl_3$), 3000 (broad), 1718 (s), 1695 (s), 1520 (s), 1345 (s), 1055 (m), 905 (w) cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}NO_6$: C, 62.01; H, 4.59; N, 4.25. Found: C, 62.06, 61.74; N, 4.75, 4.47; N, 4.40, 4.47

Resolution of α-(2-Methyl-5-nitrophenyl)ethyl Hydrogen Phthalate

In a typical resolution, 0.543 g (1.65 mmole) (±)-77 and 0.200 g (1.65 mmole) (-)-78 were dissolved in 5 ml. methanol. Ether, 75 ml., was added and the resulting solution cooled at - 10° overnight to precipitate 0.356 g of the less soluble diastereoisomer 79: m.p. 166 - 167°; $[\alpha]_{436}^{RT}$ - 12.0° (c 1.52, methanol). Two recrystallizations gave the salt m.p. 167°, $[\alpha]_{436}^{RT}$ - 15.0° (c 1.0, methanol). Further recrystallizations resulted in slightly decreased specific rotations. This less soluble diastereoisomer was dissolved in a small amount of methanol and the solution acidified with dilute HCl. The liberated hydrogen phthalate was extracted with ether. The extracts were washed, with ether, dried and concentrated. The residue was crystallized from benzene-Skellysolve B to yield 0.0932 g (-)-77: m.p. 75°; $[\alpha]_{436}^{RT}$ - 165° (c 0.932, $CHCl_3$). In similar resolutions, maximizations of the specific rotations also occurred. The (-)-77 isolated from the less soluble diastereomers after the rotations had maximized, all had rotations $[\alpha]_{436}^{RT}$ ca. - 160 to - 165°, even though the salts had rotations $[\alpha]_{436}^{RT}$ - 15 to - 19°.

From several mother liquors of the crystallizations of the less soluble diastereoisomer was obtained the more soluble diastereoisomer 80: m.p. 150°; $[\alpha]_{436}^{RT}$ ca. 0° (c 1.86, methanol). The optically impure (+)-77, $[\alpha]_{436}^{RT}$ + 132° (c 4.43, $CHCl_3$), was isolated after acidification of a solution of 80 and subsequent workup. The optically pure (+)-77 was obtained by resolution of 0.529 g (1.56 mmole) of the impure with 0.197 g (1.63 mmole) (+)-78 in a manner similar to that for the

racemic material. The less soluble diastereoisomer, m.p. 167°, $[\alpha]_{436}^{RT}$ + 14.1° (c 1.03, methanol), obtained was converted back to its hydrogen phthalate to yield 0.252 g (+)-77: m.p. 74°; $[\alpha]_{436}^{RT}$ + 164° (c 0.956, $CHCl_3$).

The N.M.R. and Infrared spectra of these resolved hydrogen phthalates were superimposible with those for the racemic compound. Neither isomer gave, however, proper microanalysis.

(-)-α-(2-Methyl-5-nitrophenyl)ethyl Alcohol ((-)-51)

A 0.125 g (0.381 mmole) quantity of (-)-77, $[\alpha]_{436}^{RT}$ - 160° (c 1.25, $CHCl_3$), was dissolved in 9.1 ml. 1.25 N sodium hydroxide (11.4 mmole) and the solution heated on a steam bath for 5 minutes. The mixture was cooled and extracted with ether several times. The ether extracts were washed with water, dried over magnesium sulfate and concentrated. The residue was chromatographed on a short alumina column with 50:50 benzene-ether solvent mixture to remove some red impurities. The eluate was concentrated and the residue crystallized from benzene-Skellysolve B solvent mixture to yield 0.047 g (0.26 mmole, 68.3%) (-)-51: m.p. 67°; $[\alpha]_{436}^{RT}$ - 150° (c 0.47, $CHCl_3$). Further crystallization failed to change the specific rotation. Extending the hydrolysis time to 20 minutes did not change the yield or specific rotation of the recovered alcohol. The N.M.R. and Infrared spectra of this alcohol were superimposible upon those for its isomers.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.64; H, 6.12; N, 7.76. Found: C, 59.62, 60.06; H, 5.78, 6.34; N, 7.76, 7.36.

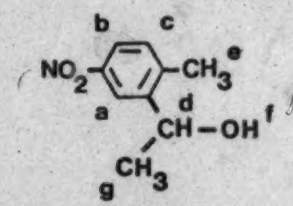
(+)-α-(2-Methyl-5-nitrophenyl)ethyl Alcohol ((+)-51)

Treatment of 0.243 g (0.735 mmole) (+)-77, $[\alpha]^{RT}_{436}$ + 164° (c 0.956, $CHCl_3$) in a manner similar to that described for its enantiomer gave after workup 0.0901 g (0.498 mmole, 67.8%) (+)-51: m.p. 66 - 67°; $[\alpha]^{RT}_{436}$ + 150° (c 0.858, $CHCl_3$).

Table XX summarizes the data for the N.M.R. spectrum of (±)-51 in the presence of added Eu(hfbc)$_3$. The shift analysis for each of (+) and (-)-51 resulted in a spectrum showing the presence of one enantiomer, i. e. only one α-methyl doublet.

TABLE XX

EFFECT OF ADDED Eu(hfbc)$_3$ ON THE N.M.R. SPECTRUM OF (±)-α-(2-METHYL-5-NITROPHENYL)ETHYL ALCOHOL (51) IN $CDCl_3$[a]



Proton	LIS, ppm[b]	Δν, ppm
a	2.29	0
b	0.46	0
c	0.45	0
d	2.54	0.06
e	0.74	0.02
f	not observed	
g	2.97	0.12

a: 0.04 M Eu(hfbc)$_3$; 0.25 M 51; molar ratio 0.167.

b: Spectrum recorded on a Varian A-60 Spectrometer.

(±)-α-(2-Methyl-5-nitrophenyl)ethyl Tosylate ((±)-81)

The alcohol (±)-51 (0.0485 g, 0.268 mmole) and 0.513 g (0.270 mmole) tosyl chloride were dissolved in 0.26 ml. dry pyridine and the solution cooled at - 10° for 40 hours. The reaction mixture was poured into cold dilute HCl and the resulting mixture extracted with ether. The ether extracts were washed with 5% sodium bicarbonate, water, dried over magnesium sulfate and concentrated. The N.M R. spectrum of the residue indicated the presence of 63% tosylate 81, 23% alcohol 51 and 14% chloride 82 as gauged by the integrations of their respective α-methyl doublets at δ 1.63, 1.46 and 1.90. Two crystallizations of the evaporation residue from benzene-Skellysolve B solvent mixture gave the pure tosylate (±)-81: m.p. 92 - 94°; N.M.R. ($CDCl_3$), δ 8.24 - 7.05 (m, 7H), 5.92 (q, J = 7.0 cps, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 1.61 (d, J = 7.0 cps, 3H).

(-)-α-(2-Methyl-5-nitrophenyl)ethyl Tosylate ((-)-81)

The alcohol (-)-51 (0.167 g, 0.92 mmole) and 0.184 g (0.966 mmole) tosyl chloride were dissolved in 0.85 ml. dry pyridine. The solution was seeded with a crystal of pyridinium hydrochloride and cooled at - 10° for three days. Following a workup procedure as described for the preparation of the racemic compound, the crude was crystallized twice from benzene-Skellysolve B solvent mixture to yield 0.124 g (0.369 mmole, 40%) (-)-81: m.p. 103 - 104°; $[\alpha]_{436}^{RT}$ - 350° (c 1.24, benzene). Its N.M.R. spectrum was superimposible with that of its racemate.

Anal. Calcd. for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18; S, 9.56. Found: C, 57.12, 57.63; H, 5.51, 5.26; N, 4.21, 3.75; S, 9.68, 9.41.

(+)-α-(2-Methyl-5-nitrophenyl)ethyl Tosylate ((+)-81)

A 0.078 g (0.435 mmole) quantity of (+)-51 was treated with 0.0844 g (0.443 mmole) tosyl chloride in 0.42 ml. dry pyridine at - 10° for 57 hours. The crude was isolated as described for the racemate and crystallized three times from benzene-Skellysolve B solvent mixture to yield 0.0536 g (0.16 mmole, 36.8%) (+)-81: m.p. 103 - 104°; $[\alpha]_{436}^{RT}$ + 352° (c 0.533, benzene). The N.M.R. spectrum of this material was superimposible with that of its racemate.

(+) and (-)-Methyl α-(2-Methyl-5-nitrophenyl)ethyl Sulfide ((+) and (-)-34)

To a flask fitted with a dry-ice cold-finger condenser was added successively a sodium ethoxide solution at 0° (from 0.0706 g sodium (3.07 mmole) in 10 ml. 95% ethanol), 2 ml. methanethiol and finally 0.164 g (0.49 mmole) (-)-81 dissolved in 2 ml. methylene chloride. After four hours stirring, the reaction mixture was diluted with water and extracted with methylene chloride. The extracts were dried over magnesium sulfate and concentrated to yield 0.0963 g (0.46 mmole, 93%) crude sulfide 34. The crude, $[\alpha]_{436}^{RT}$ + 242° (c 0.96, CH_2Cl_2), was crystallized from Skellysolve B to yield 0.0656 g (+)-34: m.p. 29 - 30°; $[\alpha]_{436}^{RT}$ + 266° (c 0.656, CH_2Cl_2). In a similar manner, the crude sulfide (-)-34, $[\alpha]_{436}^{RT}$ - 256° (c 0.534, CH_2Cl_2), was obtained from (+)-81. The N.M.R. and Infrared spectra of these enantiomers were superimposible upon those for their racemate.

(+) and (-)-Methyl α-(2-Methyl-5-nitrophenyl)ethyl Sulfone ((+)-(-)-54)

A 0.0656 g (0.31 mmole) quantity of (+)-34, $[\alpha]_{436}^{RT}$ + 266° (c 0.656, CH_2Cl_2), was oxidized with 0.104 g (1.25 mmole) 30% H_2O_2 in 3 ml. acetic acid in a manner similar to that for the racemic sulfides to provide 0.0843 g (0.347 mmole, 112%) crude non-crystallized (+)-54, $[\alpha]_{436}^{RT}$ + 152° (c ca. 0.756, $CHCl_3$, based on 100% yield). The crude sulfone was crystallized from benzene-Skellysolve B solvent mixture to yield 0.072 g (0.296 mmole, 95.5%) (+)-54; $[\alpha]_{436}^{RT}$ + 149° (c 0.72, $CHCl_3$). The enantiomeric purity of this material was determined to be 86.0 ± 1.0% using the technique described earlier for the enantiomeric purity estimations involving active sulfones derived from the Sommelet rearrangements. Several recrystallizations of (+)-54 from hot benzene cooled to room temperature failed to raise the rotation beyond $[\alpha]_{436}^{RT}$ + 155° (c 0.21, $CHCl_3$). Based on the enantiomeric purity estimation, the absolute rotation of the sulfone is calculated to be $[\alpha]_{436}^{RT}$ 173°.

In a similar preparation, 0.0534 g (0.253 mmole) (-)-34, $[\alpha]_{436}^{RT}$ - 256° (c 0.534, CH_2Cl_2), was oxidized with 0.118 g (1.01 mmole) 30% H_2O_2 in 3 ml. acetic acid at 100° for three hours. After workup, 0.055 g (0.266 mmole, 89.3%) crude non-crystallized (-)-54, $[\alpha]_{436}^{RT}$ - 145° (c 0.55, $CHCl_3$), was obtained. The enantiomeric purity of this crude sulfone was determined to be 94.1 ± 0.3% using the techniques described earlier. The sulfone was crystallized from an N.M.R. solution containing the shift reagent upon the addition of excess Skellysolve B to yield 0.0474 g (-)-54; m.p. 165 - 166°; $[\alpha]_{436}^{RT}$ - 163° (c 0.474, $CHCl_3$). Based on the enantiomeric purity

estimation and assuming there to be no fractionation during the crystallization process, the absolute rotation of the sulfone 54 is again determined to be $[A]^{RT}_{436}$ 173°. The spectral properties of these sulfones were identical with those for their racemate.

Attempted Preparation of α-(2-Methyl-5-chlorophenyl)ethyl Brosylate

A 0.0825 g (0.484 mmole) quantity of 60 and 0.130 g (0.530 mmole) p-bromobenzenesulfonyl chloride were dissolved in 0.46 ml. pyridine and the solution let stand at - 10° for 48 hours. Following the workup procedure as described for the preparation of 81, the material that was obtained was exclusively α-(2-methyl-5-chlorophenyl)-ethyl chloride (82); N.M.R. ($CDCl_3$), δ 7.55 (s, 1H), 7.15 (s, 2H), 5.30 (q, J = 7.0 cps, 1H), 2.38 (s, 1H), 1.85 (d, J = 7.0 cps, 1H). No pyridinium hydrochloride precipitated from the pyridine solution. In a repetition of this experiment with a seed of pyridinium hydrochloride added, no crystal growth was observed.

α-(2-Methyl-5-chlorophenyl)ethyl Hydrogen Phthalate (83)

The alcohol 60 (2.02 g, 11.9 mmole) and 1.75 g (11.8 mmole) phthalic anhydride were heated in 20 ml. pyridine on a steam bath for 90 minutes. The reaction mixture was cooled, diluted with 25 ml. acetone, neutralized with cold concentrated HCl and water added to the resulting solution to precipitate an oil which solidified on cooling at - 10°. The precipitate was isolated, dried and recrystallized from chloroform-Skellysolve B solvent mixture to yield 2.54 g (7.96 mmole, 66.4%) 83; m.p. 121 - 123°; N.M.R. ($CDCl_3$), δ 12.06 (s, 1H), 8.11 - 7.41 (s, 5H), 7.13 (s, 2H), 6.33 (q, J = 7.0 cps, 1H), 2.39 (s, 3H), 1.62 (d, J = 7.0 cps, 3H); Infrared (nujol),

3000 (broad), 1735 (s), 1675 (s), 1595 (s), 1575 (s), 1375 (s), 900 (w), 890 (s), 850 (w), 750 (m) cm^{-1}.

Resolution of α-(2-Methyl-5-chlorophenyl)ethyl Hydrogen Phthalate ((±)-83)

Resolution was accomplished by the fractional crystallization of the salt prepared from 1.35 g (4.24 mmole) (±)-83 and 0.514 g (4.25 mmole) (-)-78 from methanol-ether solvent mixture. The less soluble diastereoisomer, 0.817 g, m.p. 159 - 161°, $[\alpha]_{365}^{RT}$ + 118° (c 1.01, methanol), was recrystallized twice to give 0.548 g material, $[\alpha]_{365}^{RT}$ + 150° (c 0.773, methanol). The less soluble diastereoisomer was decomposed in methanol by the addition of dilute sulfuric acid to yield after the usual workup as described for the isolation of 77 0.335 g (-)-83: $[\alpha]_{436}^{RT}$ - 37.2° (c 1.30, $CHCl_3$). From the decomposition of the more soluble diastereoisomer isolated from the evaporation residue of the original mother liquor was obtained 0.567 g of semi-solid (+)-83. The optical purity of this material was increased by resolution with (+)-78 as the less soluble diastereoisomer, $[\alpha]_{365}^{RT}$ - 136° (c 1.39, methanol). Decomposition of this isomer yielded (+)-83: $[\alpha]_{365}^{RT}$ + 37.6° (c 1.26, $CHCl_3$). Further characterization of these hydrogen phthalates was not done.

α-(2-Methyl-5-chlorophenyl)ethanethiol ((±)-84)

A 5.0 g quantity (0.0214 mole) of 61 was added to 50 ml. of a 1.3 N potasium hydroxide solution saturated with hydrogen sulfide. This solution was stirred for 90 minutes at room temperature, diluted with water and the resulting mixture extracted with ether several times. The ether extracts were washed with water, dried over magnesium sulfate and concentrated. The residue was distilled under reduced pressure to yield 2.56 g (0.0137 mole, 64%) (±)-84; b.p. 105 - 107° (6 mm); η_D^{20} = 1.5736; N.M.R. ($CDCl_3$), δ 7.43 (s, 1H), 7.07 (m, 2H), 4.33 (pentet, J = 6.0 cps, 1H), 2.34 (s, 3H), 1.87 (d, J = 6.0 cps, 1H), 1.64 (d, J = 7.0 cps, 3H); Infrared (neat), 2975 (m), 2550 (w), 1595 (m), 1490 (s), 1450 (m), 810 (s) cm^{-1}.

Anal. Calcd. for $C_9H_{11}ClS$: C, 57.90; H, 5.94; Cl, 18.99; S, 17.17. Found: C, 57.90, 58.36; H, 6.00, 6.09; Cl, 19.15, 19.32; S, 16.81, 16.72.

α-(2-Methyl-5-chlorophenyl)ethyl Hydrogen Thiolphthalate ((±)-85)

The thiol (±)-84 (2.29 g, 12.2 mmole) and 1.83 g (12.3 mmole) phthalic anhydride were dissolved in 20 ml. dry pyridine and the solution heated on a steam bath for one hour. The reaction mixture was cooled, neutralized with cold dilute HCl and the resulting mixture extracted with ehher. The ether extracts were dried and concentrated to yield a residue containing a 3/2 mixture of thiolphthalate to thiol. An ether solution of the residue was washed several times with 5% sodium bicarbonate solution. The bicarbonate layers were neutralized with dilute HCl and extracted with ether several times. The ether extracts were dried over magnesium sulfate and concentrated. The solid residue was titurated in 10 ml. $CHCl_3$

and the mixture filtered to remove phthalic acid. The evaporation residue from the mother liquor was crystallized from benzene-Skelly-solve B solvent mixture to yield 0.809 g (2.42 mmole, 19.8%) (±)-85: m.p. 110 - 111°; N.M.R. ($CDCl_3$), δ 12.40 (s, 3H), 8.11 - 7.02 (m, 7H), 5.11 (q, J = 7.0 cps, 1H), 2.40 (s, 3H), 1.76 (d, J = 7.0 cps, 3H); Infrared ($CHCl_3$), 3000 (broad), 1700 (s), 1670 (s), 1290 (s), 1200 (s), 915 (s) cm^{-1}.

Attempted Resolution of α-(2-Methyl-5-chlorophenyl)ethyl Hydrogen Thiolphthalate

The attempted resolution of 0.689 g (2.06 mmole) (±)-85 with 0.258 g (2.13 mmole) (-)-78 gave as the first set of crystals from acetone-ether solvent mixture 0.274 g material: m.p. 137°; N.M.R. (acetone-d_6), δ 9.75 (s, 1H), 8.23 - 7.04 (m, 10H), 5.28 (broad, 1H), 1.54 (d, 3H); Infrared (nujol), 3250 (s), 3000 (broad), 1690 (s), 1635 (s), 1530 (s), 1290 (s) cm^{-1}. This material was void of the necessary α-arylethylthiol functionality and was likely (-)-α-phenylethyl hydrogen phthalamide (reported m.p. 133° (99)). The evaporation residue of the mother liquor smelled of a sulfur derivative. Its N.M.R. spectrum showed only three singlets at δ 2.67, 2.22 and 1.28 in the integration ratio 2:3:6 respectively with a complete absence of the necessary aromatic protons of the system. Similar decomposition occured when the resolution was attempted with brucine.

(-)-Menthyl Chloroformate (86)

To an ice-cold phosgene solution, prepared by condensing 88 g (0,90 mole) phosgene in 160 ml. cold benzene, a solution of 70 g (0.45 mole) (-)-menthol in 110 ml. benzene and 37 ml. (0.46 mole) pyridine was slowly added over a period of two hours. After the addition, the solution was stirred an additional one hour then warmed to room temperature overnight while bubbling the excess phosgene through a 10% sodium hydroxide solution. The solution was poured onto 200 g ice and the mixture acidified with dilute sulfuric acid. The separated organic layer was washed with 5% sodium bicarbonate solution, water, dried over magnesium sulfate and concentrated. The residue was fractionally distilled under reduced pressure to yield 49 g 86; b.p. 79 - 80° (2 mm); 93 - 94° (6 mm); η_D^{20} = 1.4592 (reported b.p. 96° (5 mm); η_D^{20} 1.4712 (85)); $[\alpha]_{436}^{RT}$ - 78.0° (c 1.20, benzene); N.M.R. ($CDCl_3$), δ 4.43 - 4.72 (m, 1H), 2.40 - 0.60 (m, 9H), 0.92 (d, 6H), 0.81 (d, 3H); Infrared ($CHCl_3$), 1775 (s), 1460 (m), 1160 (s), 945 (s), 835 (s), 690 (m) cm^{-1}.

O-Menthyl α-(2-Methyl-5-chlorophenyl)ethyl Thiolcarbonate (87)

A 5.55 g (0.0298 mole) quantity of (±)-84 was slowly added to a suspension of 1.27 g (0.0322 mole) 57% NaH in 50 ml. ether. After hydrogen evolution had ceased, this solution was slowly added to a stirred solution of 7.53 g (0.0302 mole) 86 in 50 ml. ether. After one hour stirring at room temperature, the reaction mixture was filtered by gravity and the precipitate washed with ether several times. The mother liquor was concentrated and the traces of solvent removed under reduced pressure to yield the oily 87; $[\alpha]_{365}^{RT}$ - 147° (c 1.0, benzene);

N.M.R. ($CDCl_3$), δ 7.37 (s, 1H), 7.10 (m, 2H), 4.82 (broad, 1H), 4.75 (q, 7.5 cps, 1H), 2.39 (s, 3H), 1.67 (d, J = 7.5 cps, 3H), 1.00 - 0.65 (m, 9H), 1.26 (s, impurity); Infrared ($CHCl_3$), 1760 (m), 1680 (s), 1600 (w), 1170 (s), 1150 (s) cm^{-1}.

Resolution of O-Menthyl α-(2-Methyl-5-chlorophenyl)ethyl Thiolcarbonate

The partial resolution of 87 was accomplished by the column chromatography of 5 g quantities on 88 g Alumina oxide (Woelm neutral, activity one). While collecting 50 ml. fractions, 700 ml. Skellysolve B was eluted through the column. The first fraction contained the oil impurity from the sodium hydride (zero rotation). Subsequent fractions contained the faster-eluting thiolcarbonate with rotations decreasing from $[\alpha]^{RT}_{365}$ - 370 to - 227° (c 0.3 - 1.0, benzene). Eluting with 700 ml. benzene removed materials of specific rotations $[\alpha]^{RT}_{365}$ - 143 to - 50.8° (c 0.3 - 1.0, benzene). Finally, the column was flushed with 500 ml. ether to give the slower-eluting thiolcarbonate of rotation $[\alpha]^{RT}_{365}$ - 13.5° (c 1.34, benzene).

Combining the middle fractions from several resolutions and rechromatographing the material as just described increased the quantities of the faster and slower-eluting fractions. The faster-eluting fraction, ca. 4 g, was rechromatographed on 70 g alumina with Skellysolve B to obtain 200 to 500 mg quantities of material with rotations ranging from $[\alpha]^{RT}_{365}$ - 281 to - 225° (c 1, benzene) from successive 50 ml. fractions. The benzene and ether fractions had rotations of $[\alpha]^{RT}_{365}$ - 180 and - 98° (c 1, benzene) respectively. Similarly, the slower-eluting fraction, ca. 4 g, was rechromatographed of 80 g alumina oxide with 1500 ml. Skellysolve B to give material with rotations from $[\alpha]^{RT}_{365}$ - 181 to - 119° (c 0.5, benzene). Eluting

with 300 ml. 1:10 benzene-Skellysolve B solvent mixture gave material with rotations of $[\alpha]^{RT}_{365}$ - 66.7 to -23.9° (c 0.5, benzene). Flushing the column with benzene then ether gave thiolcarbonate of rotations $[\alpha]^{RT}_{365}$ + 21.8 and + 17.2° (c 1, benzene) respectively.

The faster and slower-eluting thiolcarbonates had identical N.M.R. and Infrared spectra and were superimposible with those of their diastereoisomeric mixture excepting the absorption at δ 1.26 in the N.M.R. spectrum and a weak absorption at 1760 cm^{-1} in the Infrared spectrum.

(+) and (-)-α-(2-Methyl-5-chlorophenyl)ethanethiol ((+) and (-)-84)

A 0.222 g (0.60 mmole) quantity of the faster-eluting 87, $[\alpha]^{RT}_{365}$ - 281° (c 2.22, benzene) was dissolved in 5 ml. of 0.5 N sodium methoxide (2.50 mmole) and the solution heated at reflux for 90 minutes, cooled and poured into dilute sodium hydroxide. The resulting mixture was extracted with ether several times. The combined ether extracts were washed again with dilute base and the basic extracts acidified with HCl. The acidified layer was extracted with ether several times and the latter ether extracts washed with water, dried over magnesium sulfate and concentrated to yield 0.070 g (0.375 mmole, 63%) (-)-84: $[\alpha]^{RT}_{365}$ - 61.7° (c 0.7 $CHCl_3$). Concentration of the original ether extracts gave menthol.

Similarly, the (+)-84, $[\alpha]^{RT}_{365}$ + 47.7° (c 0.65, $CHCl_3$), was recovered in 54% yield from the methanolysis of 0.236 g (0.64 mmole) of the slower-eluting 87, $[\alpha]^{RT}_{365}$ - 14.7° (c 2.36, benzene), in 5 ml. of 0.5 N sodium methoxide. The N.M.R. spectrum of each isomer was superimposible upon that of their racemate.

(±)-α-(2-Methyl-5-chlorophenyl)ethyl 3,5-Dinitrothiolbenzoate ((±)-88)

The thiol 84 (0.76 g, 4.08 mmole) and 0.966 g (4.10 mmole) 3,5-dinitrobenzoyl chloride were dissolved in 2 ml. pyridine and the solution heated on a steam bath for one hour. After cooling, the reaction solution was diluted with water and the resulting mixture extracted with chloroform. The chloroform extracts were dried over magnesium sulfate and concentrated. The residue was crystallized from chloroform-Skellysolve B to yield 0.784 g material, m.p. 135 - 137°. This was recrystallized from chloroform-Skellysolve B solvent mixture, rejecting the first crop of material, to yield (±)-88; m.p. 138°; N.M.R. ($CDCl_3$), δ 9.15 (m, 3H), 7.39 (s, 1H), 7.14 (m, 2H), 5.20 (q, J = 7.0 cps, 1H), 2.43 (s, 3H), 1.78 (d, J = 7.0 cps, 3H); Infrared ($CHCl_3$), 1660 (s), 1620 (m), 1540 (s), 1340 (s), 1100 (m), 990 (m) cm^{-1}.

(-)-α-(2-Methyl-5-chlorophenyl)ethyl 3,5-Dinitrothiolbenzoate ((-)-88)

In an experiment similar to that for the preparation of (±)-88, 0.070 g (-)-84, $[\alpha]^{RT}_{365}$ - 61.7° (c 0.7, $CHCl_3$), was converted to its crude 3,5-dinitrothiolbenzoate. Crystallization of the crude from chloroform-Skellysolve B solvent mixture gave 0.0865 g (-)-88, $[\alpha]^{RT}_{436}$ - 62.8° (c 0.865, $CHCl_3$). Fractional crystallization of this material from chloroform-Skellysolve B solvent mixture gave 0.0559 g (-)-88, $[\alpha]^{RT}_{436}$ - 8.56° (c 0.56, $CHCl_3$). The evaporation residue of the mother liquor, $[\alpha]^{RT}_{436}$ - 182° (c 0.246, $CHCl_3$), was recrystallized from benzene-Skellysolve B solvent mixture to give 10.4 mg material, $[\alpha]^{RT}_{436}$ - 85.6° (c 0.104, $CHCl_3$) and an evaporation residue with a rotation of $[\alpha]^{RT}_{436}$ - 232° (c ca. 0.14, $CHCl_3$). The Infrared spectrum of this latter residue was superimposible upon that for racemic 88.

(±)-α-(2-Methyl-5-chlorophenyl)ethyl p-Nitrothiolbenzoate ((±)-89)

In an experiment similar to that for the preparation of (±)-88, 0.158 g (0.85 mmole) (±)-84 was treated with 0.160 g p-nitrobenzoyl chloride in 2 ml. pyridine for one hour at 100° to yield after workup and crystallization from benzene-Skellysolve B solvent mixture 0.222 g (0.66 mmole, 78%) (±)-89: m.p. 124 - 125°, N.M.R. ($CDCl_3$), δ 8.23 (d, J = 8.5 cps, 2H), 8.04 (d, J = 8.5 cps, 2H), 7.37 (s, 1H), 7.08 (m, 2H), 5.13 (q, J = 7.0 cps, 1H), 2.40 (s, 3H), 1.73 (d, J = 7.0 cps, 3H); Infrared ($CHCl_3$), 1660 (s), 1605 (s), 1520 (s), 1485 (s), 1350 (s), 920 (s), 865 (s), 845 (s) cm^{-1}.

(+)-α-(2-Methyl-5-chlorophenyl)ethyl p-Nitrothiolbenzoate ((+)-89)

In an experiment similar to that for the preparation of (±)-89, (+)-84, $[\alpha]^{RT}_{365}$ + 47.7° (c 0.647, $CHCl_3$), was converted to its (+)-p-nitrothiolbenzoate, $[\alpha]^{RT}_{436}$ + 36.6° (c 0.65, $CHCl_3$). Recrystallization of this material from benzene-Skellysolve B solvent mixture gave (+)-89, $[\alpha]^{RT}_{436}$ + 17.5° (c 0.63, $CHCl_3$).

(-)-Methyl α-(2-Methyl-5-chlorophenyl)ethyl Sulfone ((-)-62)

To 5 ml. of a 0.5 N sodium methoxide solution containing 0.315 g (1.69 mmole) (-)-84, $[\alpha]^{RT}_{436}$ - 51.5° (c 3.15, $CHCl_3$), obtained from the faster-eluting thiolcarbonate, was added 0.376 g (2.66 mmole) methyl iodide. After being stirred for one hour, the reaction mixture was poured into 5 ml. 10% sodium hydroxide solution and the resulting mixture extracted with ether several times. The ether extracts were washed with water, dried over magnesium sulfate and concentrated to yield 0.307 g (1.53 mmole, 90.8%) crude (-)-41, $[\alpha]^{RT}_{436}$ - 75.4°,

$[\alpha]^{RT}_{365}$ - 122° (c 3.07, benzene). The N.M.R. spectrum of this sulfide was superimposible upon that of its racemate.

The crude sulfide was treated with 0.407 g (3.47 mmole) 30% H_2O_2 in 5 ml. acetic acid for three hours on a steam bath to yield after a workup similar to that described for the isolation of the racemic sulfone 0.346 g (1.49 mmole, 97.4%) crude non-crystallized (-)-62, $[\alpha]^{RT}_{365}$ - 31.3° (c 3.46, $CHCl_3$). Fractional crystallization of the crude from chloroform-Skellysolve B solvent mixture gave (±)-62, m.p. 143 - 144°. The evaporation residue of the mother liquor was crystallized from chloroform-Skellysolve B solvent mixture to yield 0.0187 g material, $[\alpha]^{RT}_{365}$ - 10.0° (c 0.187, $CHCl_3$). The evaporation residue, $[\alpha]^{RT}_{365}$ - 113° (c 0.85, $CHCl_3$), from the latter's mother liquor was twice recrystallized from benzene-Skellysolve B solvent mixture to give 0.0678 g (-)-62; m.p. 99 - 100°; $[\alpha]^{RT}_{365}$ - 127° (c 0.60, benzene of chloroform). Further crystallizations failed to change the optical rotation of the sample. Its N.M.R. and Infrared spectra were superimposible upon those for the racemate. The optical purity of the sulfone was confirmed by observing only one enantiomer in the N.M.R. spectrum of the sulfone in the presence of the chiral shift reagent $Eu(hfbc)_3$.

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